

# Biotechnology and Healthy Ageing

POLICY IMPLICATIONS  
OF NEW RESEARCH



OECD 

# **Healthy Ageing and Biotechnology**

## **POLICY IMPLICATIONS OF NEW RESEARCH**



ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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This workshop is dedicated to the memory of Mr. Koji Ikeda who died tragically in the summer of 2000 in a car accident in France. Mr. Ikeda was First Secretary at the Japanese Delegation to the OECD, and a gifted young official of the Ministry of Health and Welfare. His energy and enthusiasm, and his deep care for the health care concerns of the elderly, made this workshop possible. Mr. Ikeda was also a dynamic participant in the health and biotechnology activities at the OECD, and his loss is felt deeply both in Japan and in the international community.

## FOREWORD

This book originated at a workshop held on 13-14 November 2000 in Tokyo. The workshop's objective was to identify the contributions of biotechnology to alleviating major age-related diseases and conditions in OECD countries. It brought together over 150 scientists, epidemiologists, industrialists, physicians and health officials working on research on the elderly and their care. The workshop brought together an interdisciplinary group of over 150 world experts in molecular biology, geriatrics, epidemiology, health economics, ethics and health policy who met for two days of very animated and fruitful discussion. Speakers were asked to identify the fields in which biotechnology is contributing most to the goal of healthy ageing and to discuss the potential social or economic roadblocks to the dissemination and use of these technologies. Their perspectives helped OECD countries understand the relative contribution that biotechnological solutions will make to the promotion of healthy ageing as compared to other possible options for prevention, care and treatment.

The workshop was convened by the OECD's Working Party on Biotechnology. It was generously sponsored by Japan's Ministry of Health and Welfare (since renamed the Ministry of Health, Labour and Welfare). Support from the European Community for the participation of European experts on healthy ageing is gratefully acknowledged. In addition, the OECD's Biotechnology Unit wishes to thank the Directorate for Education, Labour and Social Affairs for its active co-operation and support in the preparation of and follow-up to the workshop. The workshop rapporteur was Dr. Marc Weksler, of Cornell University Medical School. His expertise in gerontology was critical in identifying the major age-related diseases and conditions that are benefiting from new research.

The initial focus was on scientific contributions to healthy ageing. Promising areas of prevention and therapy include advances in biomaterials to treat mobility and frailty in the elderly, stem-cell therapies to reverse cognitive impairment, and gene therapies for cancers and heart disease. However, the most animated policy discussions at the workshop were about the future burden of disease associated with ageing populations, national differences in establishing priorities for health research and care, and the nature of the social and economic trade-offs that concerted policies for healthy ageing entail.

Part I of this publication identifies the concerns that motivated the workshop and the policy recommendations reached by the expert participants. Part II presents different perspectives on the economic impact of the ageing of OECD countries. Part III reviews the epidemiological trends behind the major age-related diseases and conditions and the most promising avenues of research for altering the prevalence of these diseases in our populations. Part IV identifies the social trade-offs that a policy for healthy ageing entail and gives a number of examples of how OECD governments are addressing these trade-offs. Finally, Dr. Salomon Wald, the previous Head of the Biotechnology Unit at the OECD, concludes with reflections on unresolved challenges to the application of biotechnology for healthy ageing.

The OECD has now embarked on a major three-year health project, which focuses on measuring and analysing the performance of health-care systems in OECD countries and factors affecting performance. The purpose is to help decision makers formulate evidence-based policies to improve the

performance of their health systems. Part of the OECD Health Project looks at the impact of new and emerging health-related technologies and examines ways in which OECD countries can best make appropriate use of health-related technology. One of the case studies envisioned involves a technology associated with an ageing-related disease.

This volume is published on the responsibility of the Secretary-General of the OECD.

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## **I. INTRODUCTION**

The increase in the human life span and the decrease in disability at older ages are a testament to the economic and social progress made in OECD countries over the course of the last century. However, while science continues to deliver an impressive supply of new treatments and interventions that will further extend healthy lives, policy makers and economists worry about the social implications of the future demand for health care. Given limited economic resources, how can the supply of and demand for health care be managed? This section summarises the positions of many contributors on the need for priority setting for the health of the elderly. Governments must simultaneously manage spending on research, long-term care, preventive and therapeutic medicines and interventions, and social integration. They need to do so in an environment where older adults have more economic power but are often marginalised. This section urges governments to evaluate the benefits of biotechnology in terms of their cost effectiveness and their contribution to quality of life.

## *Chapter 1*

### **KEY POINTS FROM THE WORKSHOP ON HEALTHY AGEING AND BIOTECHNOLOGY**

One of the greatest accomplishments of the 20<sup>th</sup> century was the enormous increase in life expectancy in the advanced countries. If present trends in fertility and life expectancy continue, between one-quarter and one-third of the population in OECD countries will be over 65 years of age by 2025. As this segment of the population is most vulnerable to chronic illness and disability, their growing numbers have profound social and economic implications. Moreover, citizens over 65 can wield significant political power, and through consumer and patient groups they are likely to demand a voice in health policy making. Not surprisingly, countries are searching for ways to promote healthy ageing.

The first objective of the workshop was to identify the opportunities created by biotechnology for understanding and ultimately slowing the ageing process. Biotechnology holds out the promise of significantly improving elderly health and quality of life by alleviating the disabling conditions which plague our later years. The workshop asked how research and development (R&D) in biotechnology can best meet the health needs of the elderly. The second objective was to assess the economic, social and ethical impact biotechnology will have on elderly health care. The novelty and cost of biotechnology-based treatments may limit their development, diffusion and use. Will biotechnology really help reduce the social challenges associated with age-related diseases? What can governments do to help to remove roadblocks to the diffusion and use of the most promising biotechnologies?

While recognising the major contribution that scientific advances can make to reducing disability, workshop speakers emphasised the need for clear efficiency and cost advantages from new technologies, given the increases such technologies imply for health expenditures. Scientists working in biotechnology identified the approaches now in the laboratory that are most likely to influence human health within 20 years. Epidemiologists discussed some of the conditions and diseases that are most prevalent and most disabling in the elderly. Health economists explored how best to evaluate the costs and benefits of various medical care strategies for the elderly and to assess their social implications. Finally, since governments face hard choices in designing healthy ageing policies, the workshop participants identified some financial, social and ethical trade-offs. Policy makers were particularly concerned with ensuring equity of access and promoting efficient and cost-effective ways of decreasing disabilities while enhancing the participation of the elderly in society.

#### **Key points of presentations**

The surprising news, according to both biologists and epidemiologists, is that the human life span continues to increase and that estimates of maximal life span may be greater than initially believed. In experimental organisms, longevity can be significantly extended through nutritional, environmental and genetic changes. In humans, evidence of declines in severe disability indicate a growing health span, although more data are needed to fully understand the cause. Medical interventions, better living

conditions and some aspects of human control over the environment share the credit for increased longevity and reduced disabilities in humans.

Biotechnologies are revolutionising the ageing experience by offering earlier diagnoses, new treatments such as regenerative and genetic interventions and ultimately disease prevention. Genomics make it possible to estimate the risk of age-related diseases. Techniques to prevent or replace lost functions are borrowing from the body's own development processes, for example, the use of pluripotent cells for cell transplants and organ regeneration, or the use of hormone therapies for lost bone and muscle mass. A variety of treatments, if not cures, will emerge as the genetic basis and the mechanisms of age-related diseases – e.g. dementia, cardiovascular disease and osteoporosis – are elucidated. In a 20-year time horizon, it may even be possible to address the fundamental causes of the ageing process and prevent or delay the onset of its most important diseases.

While science is delivering an impressive supply of lifestyle and treatment options, health economists and policy makers are concerned with the social implications of future demand. Who will bear the costs associated with new technologies? How can one ensure equity in access? Few doubt that new technologies can ultimately reduce the prevalence of disabilities in the elderly and the burden of diseases on society. However, demand for care will certainly continue to increase. As pointed out by Dr. Stefane Jacobzone, people over 65 consume three to five times more health care than those under 65, and in many countries account for about half of all health-care expenditures. Age alone does not drive costs. The countries with the most elderly are not necessarily those with the highest health or pharmaceutical expenditures. Income, supply of technologies and institutional variables play a large role in explaining aggregate variation in spending.

For all governments, the challenge is to provide better health care with limited resources and to balance cost containment, quality assurance and innovation. In making policy choices for healthy ageing, investments in high technology are often compared to existing lower-technology alternatives that may deliver significant health outcomes at lesser cost. Workshop experts explored various ways in which governments could set priorities.

Mr. Nobumichi Sakai, Director General for Science and Technology at the Ministry of Health and Welfare (since reorganised and renamed the Ministry of Health, Labour and Welfare Affairs), presented a Japanese perspective on the benefits for geriatric care of better provision and utilisation of technologies. In 2000, the Japanese government instituted a new long-term care insurance system designed to make the private sector a more important supplier of care for the elderly. This increased the incentives for using state-of-the-art treatments and technologies. In addition, on the research front, a new medical frontier strategy was initiated to find cures for cancers and heart disease, *inter alia* to help the Japanese to reach their advanced years free of debilitating physical and mental frailty. Mr. Sakai welcomed the OECD project on ageing and underscored the contribution the OECD could make to a better understanding of the economic and social impact that emerging technologies will have for the ageing populations of member countries.

Mr. Theo Vos of the Department of Human Services, Victoria, Australia, introduced the workshop to several summary measures of population health and their utility in assessing the burden of disease when governments are priority setting. Disability-adjusted life expectancy (DALE) is a measure of years lived without disability, while disability-adjusted life years (DALY) is a measure of the "health gap" or the years of life lost owing to premature mortality and "healthy" time lost owing to illness, disability and injury. For example, in Victoria, Australia, a 65-year-old woman might be expected to live a further 20 years, but on average 20% of this remaining life expectancy is lost owing to ill health. In Victoria, dementia, hearing loss, vision disorders, stroke, osteoarthritis and ischaemic heart disease are the leading causes of disability in people over 65. The ranking of the underlying

causes for DALY can give governments an indication of where potential health gains might improve DALE and help in priority setting for health services. However, Mr. Vos warned that additional cost-effectiveness studies of possible treatment would also be necessary to see what the best use of public funds might be in order to reduce age-related disabilities.

Mr. Jean-Marie Robine, from the French Institute of Health and Medical Research, discussed the explosion of the population of the "oldest old". Centenarians are expected to double in number each decade, and the natural limit to human life or "maximum longevity" is being pushed backwards as individuals survive beyond 115 years. The challenge for biotechnology is to keep the oldest old robust and vigorous for as long as possible. Strategies for bridging the gap between what the oldest old can do, could do and wish to do will require biological, social and environmental measures.

Ms. Vappu Taipale, of Finland's National Research and Development Centre for Welfare and Health, offered a national government's perspective on how countries can meet the challenge of active ageing and improve the quality of life. Active ageing means increasing the ability of people to remain productive members of society as they age. Ms. Taipale stressed that active ageing requires a multitude of government responses: *i*) the extension of working life and the reduction of age discrimination in the workplace; *ii*) improvement of the environment in which older adults live so that they do not lose function because of disability; and *iii*) innovations in prevention and care. Governments must think about how to merge health and social care services for older persons and how to create an integrated approach to prevention, cure and care. Technologies that allow older people to help themselves and help their informal caregivers are especially needed. While there is a plethora of technologies to prevent, diagnose and cure diseases and ailments, many are expensive. Governments would like to be able to identify the technologies that are most effective in reducing disability or that present significant improvements over existing therapies and treatments.

Mr. David Schlessinger of the US National Institute of Aging spoke of the importance of genetics and genomics in understanding the relationship between age and disease. Ageing, like all biological processes, has genetic determinants, and it is increasingly thought that interventions to modify age-associated disorders will depend on a better understanding of developments earlier in life, even as early as *in utero*. Recent advances in genetics and genomics, such as positional cloning, cataloguing expressed genes and the identification of markers for genetic variation in complex disorders, have been enormously important in helping researchers understand the ageing process. Studies on the onset of menopause, the development of Alzheimer's disease, the relationship of caloric restriction to longevity are examples of topics which have benefited from new genetic approaches. Genomics will permit the identification of individuals at risk of developing certain genetic, age-related disorders. In some cases, it will be possible to provide targeted treatment or reduce exposure to environmental conditions that trigger the onset of disease. The ability to identify risk factors will shift medical practice from emphasising reactive therapy to emphasising prognosis and prevention.

Mr. Calvin Harley of Geron Corporation described recent developments in the cell and molecular biology of ageing. The chronic, debilitating diseases of ageing are difficult to treat with small molecule drugs. In many cases, there is a physical loss of cells or irreversible changes in cell function. To treat conditions that plague the elderly, therefore, we must understand the mechanism of ageing in order to be able to slow the process, to rejuvenate cells or to derive new young cells. Mr. Harley outlined several theories of ageing, including: the accumulation of waste products in cells, oxidation, accumulated mutations, programmed cell death. New approaches to treating age-related conditions include: *i*) telomerase activation therapies to prevent cells from becoming senescent (or inhibition for cancer treatment); and *ii*) the use of embryonic stem cells to reprogramme and regrow degenerated cells for organs and tissues (*e.g.* for cardiovascular, liver, skin, immune and neurodegenerative disorders). Ultimately, this will lead to increased health and longer, more productive lives.

Nobel Laureate in Economics Robert Fogel, eloquently arguing that the benefits of increased expenditures on health-care services have more than justified their costs, put the economic importance of investments in health care in historical context. Over the past 300 years, humans have achieved significant control over their environment, which has enabled the species to increase average longevity by more than 100%, to increase average body size by 50% and to greatly improve physical robustness and strength. Mr. Fogel noted that technological and physical evolution are intertwined. Technical change (*i.e.* mastery over the environment) leads to physiological improvements, and, conversely, health improvements are responsible for significant advances in knowledge and accelerated technical diffusion. Economic prosperity has followed this “techno-physio” evolution: half of economic growth in Europe over the past two centuries is accounted for by increases in human energy outputs.

Mr. Fogel asked whether in the 21<sup>st</sup> century we would continue to reap economic benefits from increasing health. Over the last 100 years, both environmental improvements and advances in biomedical technology contributed to a striking decline in prevalence rates for chronic conditions. Environmental insults *in utero* and at early ages are increasingly recognised as important in predicting the later onset of chronic diseases or premature mortality. The rapid advances in public health in the first half of the 20<sup>th</sup> century should therefore contribute to a continuing decline, even an accelerating rate of decline, in the prevalence of chronic diseases in the elderly and early mortality.

Nevertheless, Mr. Fogel warned, even as the health of the elderly improves, the demand for health-care services may continue to rise, as will fiscal pressures on health-care systems. Trends in the consumption of health care over the past century clearly show that as income has increased, consumers have preferred to take an increasing share of their real income in the form of leisure, education and health. From 1875 to 1995, the share of income spent on health care increased nine-fold in the United States, from 1% to 9% of expenditures. In the United States, expenditures on health are likely to rise from their current level of 14% of GDP to 21% of GDP in 2040. Fogel argues that governments should strive to get the most out of health-care spending, rather than focus on limiting expenditures. Investments in science will have long-term pay-offs. Controlling access to new technologies will be increasingly futile in an era of global information flows and potentially detrimental both to innovation in the private sector and to public health. The policy focus of OECD countries should be on changing the methods of health-care financing and ensuring that consumers demand increasingly effective care.

While acknowledging the contributions of technology, epidemiologists and policy makers suggested that they should be assessed in terms of their cost effectiveness. This would help to determine their added value in improving health outcomes at an affordable social cost. The use of evidence-based medicine for technology assessment is an increasingly popular strategy for channelling demand and allocating resources, as it helps to screen the new technologies that significantly and efficiently improve health. Extra resources can then be spent on low-technology alternatives such as diffusion of best medical practices and promotion of changes in lifestyle. Of course, it is important not to hinder efficiency gains from new technologies and to avoid detrimental effects both to innovation in the private sector and to public health.

Other speakers assessed the contributions biotechnology is making to the detection, prevention and cure of these conditions.

### ***Progressive cognitive impairment***

Mr. Leon Thal of the University of California at San Diego spoke about advances in earlier diagnosis of Alzheimer’s disease and Phase I clinical trials for immunisation against amyloid plaques and gene therapy for the delivery of neurotrophic factors in humans. Mr. Bernd Sommer of Novartis

discussed the contribution of biotechnology to our understanding of the neurodegenerative process in Parkinson's disease. To develop effective therapies, scientists need a better understanding of the pathogenic process and animal models of the disease. Biotechnology is contributing to these goals and to the development of therapies, such as gene therapies and implantation of stem cells that have been differentiated *in vitro* into dopaminergic cells.

### ***Mobility and frailty***

Mr. David MacLean of Pfizer spoke about the challenge of restoring bone mass and preventing muscular frailty, both of which are key to reducing institutional care. Mr. MacLean identified a number of new therapies but warned that regulatory approval of new agents to maintain physical function will not be easy. Mr. Rik Huiskes of the University of Nijmegen spoke about the future of bone and joint replacement. New reconstruction methods with non-artificial tissues are being studied but success will require close collaboration among researchers in tissue engineering, biomechanics and biotechnology.

### ***Vascular disease***

Many areas of cardiovascular medicine lack effective treatment, including: myocardial revascularisation, peripheral ischaemia, angioplasty restenosis and vein graft failure. Gene therapy holds the promise of alleviating these conditions in animal models but, as Mr. Andrew Baker of the University of Glasgow noted, there are still many problems associated with gene therapy for vascular diseases, especially as regards gene delivery vectors. Vascular gene therapy is a long way from routine medical practice. Mr. Nick Freemantle of the University of York focused on the frequent misuse of prescription drugs for cardiovascular disease and argued that efforts should concentrate on creating simple standards of diagnosis and care to improve patient health.

### ***Cancer***

Mr. Michel Sadelain of Memorial Sloan Kettering Hospital spoke about the prospects of gene transfer as a therapeutic approach for cancer. Several strategies have been envisaged – cytotoxic gene delivery to kill cancerous cells, partial phenotypic correction to render cells “non-cancerous”, augmenting the immunogenicity of tumour cells, anti-angiogenic therapy to reduce vascularisation of tumours. Mr. Sadelain believes researchers are still at the stage of developing safe and efficient vectors. *In vivo* gene transfer in tumours remains a challenge.

### ***Policy considerations***

The main policy implications of new biotechnologies for the promotion of healthy ageing were of three types:

- ◆ The identification of roadblocks to the development, dissemination and use of new technologies as perceived by pharmaceutical companies, public research bodies, associations of the elderly and doctors.
- ◆ The approaches being taken to controlling access or ensuring access to new technologies, again from the perspective of various actors (*e.g.* governments, insurers and elderly rights activists).

- ♦ The identification of contributions international organisations can make to promoting healthy ageing.

Faced with a pipeline of new technologies that could revolutionise the experience of ageing – reducing both disability and disease – what decisions can governments make now to ensure that these new approaches are available, affordable and equitable? These issues indicate where the OECD can play a role in enhancing healthy ageing.

### ***New approaches to health-care consumption and financing***

As consumers become more aware of their health options, it is expected that the demand for health care will continue to increase, even if the physiological burden of age-related diseases continues to decrease. The health-care industry will also continue to be a high-growth industry well into the 21<sup>st</sup> century. Many governments and organisations already struggle to contain health costs while ensuring quality care. In this context, new technologies entail a risk of destabilising current health system and health financing arrangements. As demand rises, countries will probably want to assess the value of these technologies in terms of their cost effectiveness and contribution to quality of life. Countries may also need to reassess how their health-care costs are financed and distributed, and rethink the boundaries of public intervention.

### ***Addressing regulatory gaps***

The cost of bringing new pharmaceutical products to market is a function of the size of clinical trials required to prove safety and efficacy. A regulatory environment that is better adapted to new technologies and to the needs of the elderly might result in more affordable therapies. For drugs that target age-related conditions and diseases, one of the major hurdles has been to identify measurable endpoints in clinical trials. For preventive treatments, patients in clinical trials must be followed for many years, thus considerably raising the cost of the trials. When experimental treatments are for a condition, like frailty, which is not yet well defined, the clinical trials can be expensive because drug companies have to create new measures of efficacy. Finally, pharmacogenomics will eventually allow better targeting of patient populations, a more rational approach to care, and perhaps reduce the size of the necessary clinical trials. Regulatory authorities may need to work flexibly with biomedical industries to develop preventive measures and therapies for age-related problems in a timely, affordable manner.

Biotechnology is also developing rapidly in areas that defy current regulatory frameworks. Existing regulations may need to be revised for stem-cell research, gene delivery systems and genetic testing. Progress in these areas is of great importance to ageing research and clinical practice.

### ***Emphasise the fair and ethical treatment of the elderly***

Health-care discrimination against the elderly should be discouraged, especially with respect to the rationing of care. Access to care should be based on transparent criteria and related to need rather than age.

In many countries, there should be more extensive training in geriatrics and it ought to emphasise a preventive, life-course approach to care. Furthermore, when developing new drugs, the elderly should be better represented in clinical trials. Both reforms would improve the care the elderly receive.

Finally, the fair and ethical treatment of the elderly goes beyond narrow health care considerations to encompass spiritual and community considerations. Active ageing, the experts on ethics emphasised, is a holistic process. The elderly should be considered a resource that can contribute to society through participation in the workforce and community.

### ***Extending the ageing agenda of international organisations***

While ageing is well recognised as an issue in the advanced countries, it is also affecting the developing world. In less than 25 years, close to 60% of the world's elderly will live in Asia. These countries will be under great stress because the increase in the life span is happening more rapidly than in the OECD countries and because they will have fewer resources. For developing countries, therefore, preventive approaches to the health problems of old age are essential. International organisations need to play a role in the development and diffusion of cost-effective technologies.

International organisations can also develop indicators and share information on technologies that improve quality of life. These data will help countries assess the economic and social impact of ageing and improve the performance of the health-care system.



## *Chapter 2*

### **RAPPORTEUR'S SCIENTIFIC SUMMARY**

*by*

**Marc E. Weksler**

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We are at the beginning of the Biological Revolution. Two centuries ago, the Industrial Revolution changed the way inanimate objects were manufactured. Today, the Biological Revolution is providing the means to create novel living organisms. There are bacteria that produce novel proteins, animals that express human disease genes and, perhaps most striking, plants that have been genetically modified to grow under environmental conditions of little water, high salt or endemic parasitic diseases, conditions that limit the growth of crops and cause starvation in many parts of the world.

In the coming decades, advances in genomic analysis and genetic therapy will bring even greater benefits to human populations. As with all revolutions, there are potential dangers inherent in the new technologies, but if these are sensibly regulated and wisely applied, their benefits should far outweigh their risks. There is every reason to believe that the elderly will benefit from these new technologies.

In his introduction to the OECD Workshop on Biotechnology and Healthy Ageing, Dr. Nobumichi Sakai noted the Japanese Prime Minister's commitment to have Japan take the initiative in applying technology to the biology of ageing. Mr. Risaburo Nezu described in greater detail how gene therapy, regenerative medicine and biomaterial technology would enrich geriatrics and support the aspirations of the elderly by controlling disabling diseases that limit the enjoyment of later life.

It is not the purpose of this summary to provide a comprehensive overview of discussions that took place over two days of discussion. Rather, it attempts to highlight some concepts which the rapporteur found particularly interesting. Professor Robert Fogel introduced the notion of "technophysiological" evolution, which he defined as society's progressive mastery of its environment. Humans have taken control of many aspects of their environment thanks to the Agricultural Revolution and the Industrial Revolution and are now, with the Biological Revolution, poised to take control of life itself. Professor Fogel presented data showing how the number of hours an individual worked to obtain sufficient food has decreased by 90% since the Industrial Revolution. Like all new technologies, these advances have also engendered new problems. The worldwide epidemic of obesity is one of these and results from a caloric intake which exceeds the number of calories required for adequate nutrition. Professor Fogel cited recent studies that environmental "traumas" early in life, together with genetic inheritance, contribute to disability late in life. Foetal exposure to tobacco, alcohol or dietary deficiency as well as disease genes cause long-lasting effects leading to late-life disability and disease.

Professor Fogel then turned to the problem of rising health-care costs due to advances in health care. While many governmental officials wish to contain health-care costs, he argued that most populations in developed countries wish to spend more on health. In his opinion, most elderly people would rather have "a new knee than a new Honda". In his view, health-care costs are driven to a considerable extent by increasing demand, not only by the increasing supply of new medical services.

Dr. Stephane Jacobzone pointed out that the costs of long-term care are a sizeable fraction of total health-care expenditures and are almost exclusively for the elderly. However, as high levels of health-care expenditures weigh on the economic balance of health systems, investments in biotechnology should aim at lowering late-life disease and disability to deliver value for money in improving quality of life.

What diseases and disabilities of the elderly population should be given research and therapeutic priority? Dr. Theo Vos discussed the concept of "burden of disease". His view is that the impact of disease on society is better judged by its economic cost than the mortality rate. Like Professor Fogel, he pointed to "lifestyle" influences, such as poor nutrition, use of tobacco and lack of exercise, as major contributors to disability and disease among the elderly. Considerable research will be necessary to discover the molecular basis for benefits associated with exercise, good nutrition and avoidance of tobacco and alcohol. It is not too much to hope that the Biological Revolution will provide a means, perhaps a pill, that mimics the effects of exercise or blocks the harmful effects of food and tobacco.

Advances in the biology of ageing were discussed in considerable detail. Dr. Jean-Marie Robine reported a surprising conclusion from recent demographic studies that have forced a reconsideration of the view that maximal life span is fixed. Some studies of the increasing life span of human populations in developed countries suggest that maximal life span may not be fixed but established by the increasing statistical risk of dying with increasing age. These data are consistent with an increase in the maximal life span of humans.

Dr. Calvin Harley, Scientific Director of the Geron Corporation, a biotechnology company that devotes significant resources to the health and welfare of the elderly, discussed two biological phenomena linked to the biology of ageing and ultimately to the health of the elderly. The first is the generation of free radicals. Free radicals are by-products of oxidative metabolism that damage cellular DNA, lipids and proteins. These effects have been shown to correlate with the health and life span of many organisms, and the introduction of genes that produce scavengers of free radicals has been shown to extend the life span in lower organisms. In humans, the contribution of free radicals to diseases of ageing such as cancer, atherosclerosis, macular degeneration and Alzheimer's disease is being actively studied.

In addition to neutralising free radicals, benefits may be derived from decreasing their production. Caloric restriction is the only strategy that extends maximal life span of all species tested. Fewer free radicals are produced when caloric intake is restricted, and animals whose caloric intake is limited to 40% to 50% of intake when food is freely available have dramatically prolonged life spans. Individuals do not find acceptable the degree of caloric restriction necessary to achieve these effects. However, Dr. David Schlessinger suggested that with an understanding of molecular mechanisms, specifically which genes are turned on and which genes are turned off by caloric restrictions, drugs may be developed that mimic the effects of caloric restriction that lead to improved health and longer life.

The second avenue of research discussed by Dr. Harley was the shortening of the telomeres located at the ends of chromosomes. These elements appear to regulate the life span of proliferating cells in culture. Because few normal cells express telomerase, the enzyme that maintains telomere

length, most normal cells have a finite life span. In contrast, most immortal cells, such as cancer cells and stem cells, express telomerase, maintain their telomere length and retain the capacity to divide. Regulating telomerase and thereby telomere length may permit non-immortal cells to live longer and avoid senescence and conversely may convert cancer cells to cells with a finite life span leading to their disappearance.

The remarkable promise of pharmacogenomics was described by Dr. Lefkos Middleton not only in terms of developing new targets for drug action but also of matching individual patients to specific therapies. Grouping patients by genetic characteristics of disease will also allow smaller clinical trials. Instead of the thousands of patients now required to test clinical efficacy, it will be possible to prove clinical efficacy by testing hundreds of patients who share genetic factors. In this way, promising drugs will come to market more quickly and at lower cost. By taking into account patients' genetic composition, drugs can be given to patients for whom the medication will be effective and not given to patients for whom it will not. An example of a pharmacogenomic approach to clinical studies was recently published (Esteller *et al.*, *New England Journal of Medicine*, 2000, 343, p. 1350). This study of the effectiveness of an alkylating drug for patients with brain cancer showed that the benefit depended upon the level of DNA repair activity that reversed the drug's effect. The patients with low DNA repair activity benefited from the alkylating agent while those with high DNA repair activity benefited significantly less. Statistically significant results were obtained from a clinical trial involving fewer than 100 patients.

Pharmacogenomics will allow for the more efficient development of new drugs and better selection of patients for treatment at reduced costs. An example of the importance of targeting drugs to appropriate patients is clearly seen when considering drug therapy for hypertension. It is estimated that 100 patients must be treated to prevent one complication from hypertension, such as stroke, heart attack or renal failure. Using the tools of pharmacogenomics, it should be possible to target anti-hypertensive drugs to patients who can respond, reducing the cost and the toxic side effects of anti-hypertensive therapy.

Drs. Albert Hofman, Leon J. Thal and Bernd Sommer reviewed the chronic neurodegenerative diseases, including Alzheimer's and Parkinson's, that cause such disability among the elderly. It is becoming increasingly clear that the neurodegenerative diseases of the elderly share one important feature, the deposition of proteins within the brain – amyloid in the case of Alzheimer's disease and synuclein in the case of Parkinson's disease. Treatment of these diseases is today directed at preserving residual brain function. In future, the goal will be to prevent or reverse the cerebral deposition of these proteins and to increase their clearance from the brain, thereby interrupting the pathogenic mechanism of disease.

Dr. Hofman provided evidence that biotechnology has allowed rapid progress in unravelling the mysteries of Alzheimer's disease. A mutant gene that causes early-onset Alzheimer's disease was discovered in 1991. By 1995, the gene had been introduced into a mouse, providing the first animal model of the disease. The availability of the "Alzheimer mouse" has made it possible to test new therapies, and in 1999 a very promising therapy was proven effective in the mouse. Immunisation of the Alzheimer mouse with the amyloid peptide prevented or reversed its deposition in the brain and the consequent loss of cognitive function. Thus, genetic analysis of human disease followed by recombinant DNA technology made it possible to develop an animal model of a human disease in eight years, which led to the development of a novel therapy which is now in clinical trials.

Geriatric disease often results in syndromes which compromise mobility and result in isolation. Dr. Stefania Maggi turned attention to diseases with low mortality but high morbidity. Diseases such as osteoarthritis and sarcopenia lead to frailty, immobility and degenerative diseases of the eye and

ear, which result in loss of sight and hearing and lead to isolation. These degenerative diseases, whose genetic basis remains for the moment elusive, contribute greatly to suffering and to the high cost of health care for the elderly, as they frequently require institutionalisation. There is however great hope for “regenerative medicine”, the replacement of malfunctioning tissues and organs by transplantation of human organs or replacement with bioengineered organs. The discovery of novel biomaterials has led to improved artificial joints. Replacement of arthritic hips and knees has “miraculously” restored the capacity to walk to many elderly persons. Older individuals, whose arthritis was so severe that their capacity to live alone was threatened and institutionalisation was being considered, regained the ability to walk and maintain their independence, without costly health expenditures for institutional care.

Progress continues to be made in the creation of artificial joints, and great progress has been made as well in creating artificial organs of far greater complexity: the artificial pancreas for diabetes and the artificial heart for patients with end-stage heart failure. Thus, technology in the pursuit of healthy ageing extends well beyond genes and recombinant DNA technology to include biomaterials and bioengineering. Information technology is also contributing to improved health care of the elderly. Dr. Alain Pompidou pointed out the vital role that informatics will play in maintaining good health by establishing early diagnosis and allowing the elderly to remain in their homes without being isolated thanks to telemedicine.

Finally, there was productive discussion about building partnerships between the public and private sectors in realising the promise of the Biological Revolution for the elderly. Together, public and private efforts based on high technology can provide greater health for the elderly at lower costs. Greater expenditure to maintain good health is not merely a humane and an ethical decision but also a wise economic strategy. Maintaining health is far less expensive than treating disease. Consider the cost savings that followed the discovery of the preventive vaccine for poliomyelitis. The cost of developing and administering an effective vaccine was far lower than the cost of providing chronic care to patients who developed the disease.

Health maintenance and disease prevention are what our society desires. This strategy is always a “good buy”. It seems appropriate to conclude by repeating the comment made by Mr. Nezu in opening the workshop: that technology applied to geriatric medicine not only responds to the aspirations of the elderly by providing the best hope for preventing or reversing the diseases and disabilities of ageing, it will also reduce health-care costs.

## II. THE ECONOMICS OF HEALTHY AGEING

There has long been concern over the affordability of OECD health-care systems. In part, these concerns are based on the notion that health-care costs rise with age. This section examines economic issues relating to ageing populations and dispels some of the myths. The empirical evidence presented suggests that ageing, by itself, is unlikely to lead to escalating health costs.

The key message from this section is that the policy challenge posed by ageing is to provide effective, efficient and appropriate health and social care services. The policy goal is to provide services that give value for money and are in line with population needs and wants. As recommended by the authors in this section, this goal must be met by a greater emphasis on evidence-based policy making, especially with regard to the development, supply and diffusion of technologies.

### *Chapter 3*

## **BIOTECHNOLOGY AND THE BURDEN OF AGE-RELATED DISEASES**

*by*

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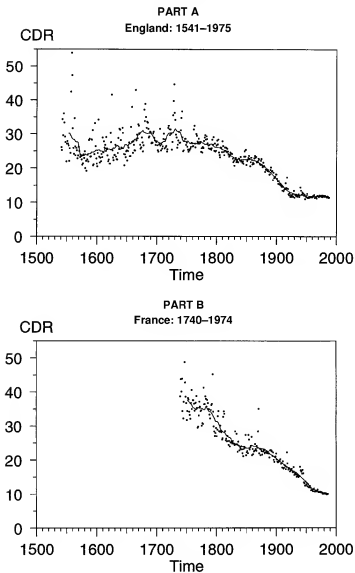
### **Introduction**

During the past two decades there have been a number of major advances in constructing time series charts of the decline in mortality in Western Europe, Japan and the United States. The data for these time series were obtained from a variety of archives. Both the retrieval and processing of the data were made possible by the remarkable advances in computer technology, which not only permitted the creation of the series but also enabled linkages to variables in order to explain improvement in health and longevity over the past three centuries. This chapter focuses first on England and France, for which data exist for the longest period of time, but also makes use of data from Sweden, Norway, the Netherlands, the United States and Japan.

Figure 1 shows a time series for the decline in mortality rates dating from the 1540s in England and the 1740s in France to the present. Two features of this figure are striking. First, it indicates that in both countries, crude mortality rates were three to four times higher in the 18<sup>th</sup> century than they are today. A second feature is the much greater year-to-year variability of mortality rates in the past, with annual death rates sometimes exceeding the secular trend by as much as 50-100%. These mortality crises were what initially caught the attention of demographers, who argued that such crises accounted for a large part of total mortality during the 17<sup>th</sup> and 18<sup>th</sup> centuries, and that the decline in mortality rates after about 1750 was largely due to the elimination of these crises (mainly the elimination of periodic famines). However, when the nation-wide time series shown in Figure 1 were partitioned, it appeared that in both France and England the elimination of crisis mortality, whether famine-related or not, accounted for only a small fraction of the secular decline in mortality rates. About 90% of the drop was due to the reduction in the "normal" levels of mortality.

Another feature of Figure 1 is the repeated interruption of downward trends in mortality, and even their reversal. Substantial interruptions and reversals in the downward trend during the 19<sup>th</sup> century have also been demonstrated for the United States, Sweden and Hungary. These lasted several decades and prevented even the keenest contemporary observers from appreciating that the growing control of the environment had the capacity to transform human physiology. It was not until the First World War that biodemographers and epidemiologists recognised they were in the midst of a long-term reduction in mortality rates that had not yet run its course.

Figure 1. Secular trends in mortality rates in England and France



CDR = crude death rate.

Note: Each diagram shows the scatter of annual death rates around a 25-year moving average.

Just how remarkable the change has been during the past three centuries is summarised by three key figures on life expectancy at birth. In France, England and a few other OECD countries, life expectancy at birth at the beginning of the 18<sup>th</sup> century was about 30 years. Today it is in the neighbourhood of 76 to 80 years in the high-income nations of the OECD. The lowest long-term life expectancy rate for *Homo sapiens* is estimated to be about 20 years. Hence over the 200 000-year history of the species, life expectancy at birth has increased by about 60 years, and five-sixths of this increase has occurred since 1700. Half of it occurred during the past 100 years.

Attempts to explain the remarkable decline in mortality rates since 1700, and the concurrent improvement in health, especially over the past century, have produced significant advances in knowledge. Although many of the new findings are still tentative, they suggest a new theory of evolution that could be called “technophysiological evolution”, a term coined by Dora Costa, an economist and biodemographer at the Massachusetts Institute of Technology, and the author.

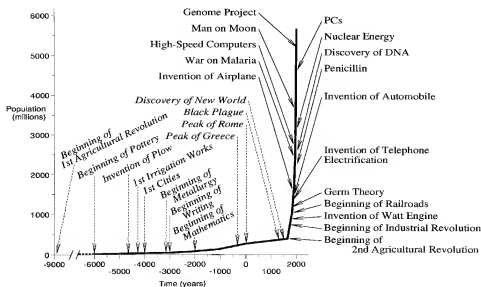
Technophysiological evolution is the result of a synergism between technological and physiological improvements. It is a form of human evolution that is biological but not genetic, rapid, culturally transmitted, but not necessarily stable. This process is still ongoing in both rich and developing countries. Unlike the genetic theory of evolution through natural selection, which applies to all of life on Earth, technophysiological evolution applies only to the last 300 years of human history, and particularly to the last century.

Human beings today have gained an unprecedented degree of control over their environment which sets them apart not only from all other species, but also from all previous generations. This new degree of environmental control has enabled *Homo sapiens* to increase its average body size by over 50%, to increase its average longevity by more than 100% and to improve greatly the robustness and capacity of vital organ systems.

Figure 2 shows how dramatic this change in control has been since 1700. During its first 200 000 years or so, the *Homo sapiens* population increased at an exceedingly slow rate. The discovery of agriculture about 11 000 years ago broke the tight constraint on the food supply imposed by a hunting-and-gathering technology, making it possible to release between 10% and 20% of the labour force from the direct production of food. This gave rise to the first cities. The new technology of food production was superior to the old and supported a much higher rate of population growth than had been the case prior to ca. 9000 BC. Yet the advances in the technology of food production after the second Agricultural Revolution (which began about 1700 AD) were far more dramatic than the earlier breakthrough and made it possible for the population to increase at exponential rates. The new technological breakthroughs in manufacturing, transportation, trade, communications, energy production, leisure-time services and medical services were in many respects even more striking than those in agriculture. If technological change has accelerated dramatically since 1700, the diffusion of modern technology has also accelerated greatly over the past two centuries. The increase in world population in the 20<sup>th</sup> century was four times as great as the increase during the whole previous history of humankind.



Figure 2. Growth of the world population and some major events in the history of technology



The most important aspect of technophysiological evolution is the continuing conquest of chronic malnutrition, which is mainly linked to a severe deficiency in dietary energy, which was virtually universal three centuries ago. In rich countries today, some 1 800 to 2 000 kcal of energy are available daily for the work of a typical adult male, age 20-39. During the 18<sup>th</sup> century, however, France produced less than one-third the current amount of energy for work, and England did not fare much better. One implication of these estimates of caloric availability is that by current standards mature European adults of the 18<sup>th</sup> and much of the 19<sup>th</sup> century must have been very small in stature and less active. Recent studies have established the link between height and weight at early ages and the onset of diseases and premature mortality at middle and late ages. Figures 3 and 4 summarise data showing the connection of height and weight to the risk of dying in American and Norwegian male cohorts. The American cohort turned 65 around 1910 and the Norwegian cohort around 1980. The two cohorts thus span most of the improvements in health and longevity over the 20<sup>th</sup> century. Yet the functions relating height and the body mass index (BMI, a measure of weight controlled for height) to the risk of dying are quite similar.

Variations in height and weight are associated with variations in the chemical composition of the tissues that make up vital organs, in the quality of the electrical transmission across membranes, and in the functioning of the endocrine system and other vital systems. Nutritional status, represented by height and weight, appears to be a critical link connecting improvements in mortality to improvements in human physiology.

Figure 3. Relative mortality risk among Union Army veterans and among Norwegian males

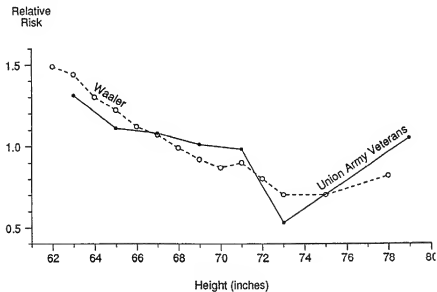
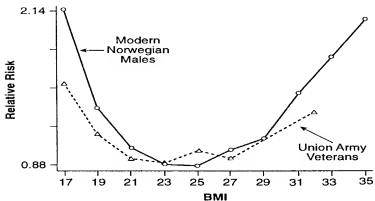


Figure 4. Relative mortality risk by body mass index among men 50 years of age Union Army veterans around 1900 and modern Norwegians



So far the discussion has focused on the contribution of technological change to physiological improvements. The process has been synergistic, however, with improvement in nutrition and physiology contributing significantly to the process of economic growth and technological progress along lines which the author has described elsewhere. The main conclusion to be drawn here is that technophysiological evolution appears to account for about half of the economic growth in Europe over the past two centuries. Much of this gain is due to the improvement in human thermodynamic efficiency. Thus, the rate of converting human energy input into work output appears to have increased by about 50% since 1790.

## Prospects for continued decline in the burden of health care

Both environmental improvements and advances in biomedical technology have contributed to a striking decline in the prevalence of chronic health conditions in high-income countries during the course of the 20<sup>th</sup> century. This development is illustrated for the United States in Table 1, which compares the prevalence of chronic conditions in Union Army veterans of the Civil War (who were 65 or older in 1910) to veterans of the Second World War who were the same ages in the mid-1980s. Even before the impact of alleviating medical intervention is considered, Table 1 shows that prevalence rates decreased by 29% to 52% over the course of the seven and a half decades separating the elderly veterans of the two wars. However, for two disorders, genito-urinary and circulatory diseases, prevalence rates were higher in the mid-1980s than in 1910.

**Table 1. Comparison of the prevalence rates of selected chronic conditions among Union Army veterans in 1910 and World War II veterans in the mid-1980s**

Disorders	Percentages				
	1 Union Army veterans	2 World War II veterans before alleviating intervention	3 Annual rate of decline in prevalence rates before alleviating intervention	4 World War II veterans after alleviating intervention	5 Annual rate of decline in prevalence rates after alleviating intervention
Musculoskeletal	67.7	47.9	0.4	42.5	0.6
Digestive	84.0	49.0	0.7	18.0	2.0
Genito-urinary	27.3	36.3	+0.4	8.9	1.5
Central nervous, endocrine, metabolic or blood	24.2	29.9	+0.3	12.6	0.9
Circulatory	90.1	42.9	1.0	40.0	1.1
Respiratory	42.2	29.8	0.5	26.5	0.6

Note: + indicates an increase in prevalence rates. The term "before alleviating intervention" in Column 2, refers to interventions that alleviated existing chronic conditions, not interventions that prevented chronic conditions from occurring, as in the use of penicillin to prevent the occurrence of rheumatic heart disease.

Medical intervention reduced prevalence rates for all six disorders. Such interventions were especially effective in chronic digestive and genito-urinary disorders, where prevalence rates were cut by 60% and 70%, respectively. In the cases of musculoskeletal, circulatory and respiratory disorders, the main impact of medical intervention has been to reduce the severity of the condition rather than to eliminate it. Whether the medical interventions cured disorders or merely attenuated them, they contributed to extending the duration of chronic conditions by postponing death. In other words, medical intervention appears to have had the ironic effect of increasing the duration of some disorders.

It is not yet certain whether environmental improvements and medical interventions have reduced or increased the overall average duration of chronic diseases over the course of the 20<sup>th</sup> century. Preliminary analysis indicates that the average age of onset of chronic disorders among veterans of the Union Army may have begun about five years earlier than among veterans of World War II. This effect is partly offset by an extension in life expectancy at age 50 by three years for the latter veterans. Partitioning the decline in prevalence rates into environmental effects and medical intervention effects is quite complex because of the long-term effects of nutritional and other biomedical insults at earlier ages on the odds of developing chronic diseases at middle and late ages. Although such lifelong effects have been suspected in particular diseases, it is only recently that a substantial body of evidence bearing on the interconnections has been amassed. Longitudinal studies connecting chronic diseases at maturity, middle age and late age to conditions *in utero* and infancy were reported with increasing frequency in the 1980s and the 1990s. The exact mechanisms by which malnutrition and environmental insults at early ages affect waiting time before the onset of chronic diseases are still unclear, but it seems reasonable to infer that environmental insults during the period when cell growth is rapid could lead to long-lasting impairment of vital organs.

The connections between alcoholic consumption or smoking during pregnancy and the damaging of the central nervous system of foetuses were established by the early 1980s. Evidence of protein-calorie malnutrition (PCM), which was shown as early as 1968 to cause permanent impairment of the central nervous system function, continued to accumulate in the 1990s. Recent evidence also indicated that iodine deficiency, both *in utero* and during infancy, can also cause permanent neurological damage.

Perhaps the most far-reaching studies linking early-age insults and chronic conditions at later ages were those undertaken by the Environmental Epidemiological Unit of the British Medical Research Council at the University of Southampton. They reported that conditions such as coronary heart disease, hypertension, stroke, type II diabetes and auto-immune thyroiditis began *in utero* or in infancy, but did not become apparent until mid-adult or later ages. Although results were questioned during the first half of the 1990s, there was a substantial expansion of research into the connection between experiences before the age of one and the subsequent chronic diseases (or premature mortality) during the second half of the decade. The strongest evidence for such links that has emerged thus far pertains to hypertension, coronary heart disease (CHD) and type II diabetes. A review of 32 papers dealing with the relationship between birth weight and hypertension concluded that there was a significant tendency for blood pressure at middle age to increase as birth weight declined. Evidence of a connection between anthropometric measures of the neonate and later CHD has been found by investigators in Finland, India and Sweden.

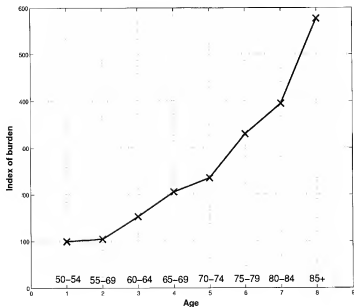
The conclusion that environmental insults *in utero* and in early life are linked to the later onset of chronic diseases suggests that the rapid advances in public health technology between 1890 and 1950 contributed to the continuing decline in the prevalence of chronic diseases during this period. The first half of the 20<sup>th</sup> century witnessed an avalanche of new technologies that improved the environment, including purification of water and milk supplies, widespread draining of swamps, improvement of garbage disposal and sewage systems, rapid reduction in the use of animals (especially in the city) for transportation, the switch to electricity and to fuels with a lower carbon content and rapid advances in obstetric technology and neonatal care. This period also saw significant improvements in the diversity of the food supply available throughout the year and the beginnings of dietary supplements to improve the consumption of vitamins and other trace elements.

Evidence that these changes had an effect on longevity during middle and late ages is contained in a recent study undertaken at the Max Planck Institute for Demographics Research in Rospock, Germany. This study found strong correlations between month of birth and longevity samples of

middle-aged men from Austria, Denmark and Australia. The connection appears to be related to the relatively poor quality of the diet available to mothers during winter months in the first third of the 20<sup>th</sup> century. Using correlation analysis and other statistical techniques, the study concludes that approximately one-third of the variance in longevity after age 50 was due to environmental influences during the months following conception. Very similar results have been found for the Union Army veterans who were born two generations earlier.

Evidence that the rate of decline in disability may be accelerating has been reported by investigators at the Center for Demographic Studies at Duke University, who have made use of data obtained from national long-term care surveys conducted between 1982 and 1994. This study reported an average annual decline of 1.3% in disability rates during the 12-year period. However, when this period was broken into two parts, there was a statistically significant acceleration in the rate of decline during the second part of the period. The study attributed improving health to changes in socio-economic factors, including the level of education, in the first half of the 20<sup>th</sup> century.

Figure 5. Relative burden of health care by age, US data circa 1996



Note: Average burden of 50-54 year olds = 100.

Does the mounting evidence that the long-term and possibly accelerating decline in the prevalence of chronic diseases mean that the “supply” of treatable chronic diseases is declining? The word “supply” is employed here to distinguish the physiological burden of health care from the demand for health-care services, which may rise even if the physiological burden remains constant or declines. Moreover, the exact sense of “burden of disease” as used here differs from the definition employed by the World Health Organization (WHO) and the World Bank, which treat death as the maximum burden of disease, rightly so from an ethical standpoint. However, from a financial

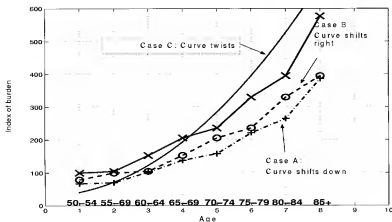
standpoint, death terminates health-care expenditures for a particular individual. Consequently, to address the question of whether declines in physiological prevalence rates will relieve current fiscal pressures on the health-care systems of OECD member countries, it is necessary to weight the existence of a particular chronic disease by factoring in the cost of treating that condition, which generally increases with age.

Such an index is shown in Figure 5. In this index, based on US data, the burden of per capita health-care costs is standardised at 100 for ages 50-54. Figure 5 shows that the financial burden of health care per capita rises slowly during the sixth decade of life and accelerates progressively during the seventh, eighth and ninth decades of life. The health-care cost per capita at age 85 and over is nearly six times that between ages 50 and 54. It is also noteworthy that the financial burden of health care for ages 85 and over is more than 75% higher per capita than at ages 75-79. However, the physiological prevalence rate (number of conditions per person) is roughly constant at age 80 or more.

Costs rise even though the number of conditions per person remains constant because the severity of the conditions increases and because the cost of preventing further deterioration, or even partially reversing deterioration, increases with age. It should be kept in mind that standard prevalence rates merely count the number of conditions, neglecting both the increasing physiological deterioration with age and the rising cost of treatment per condition. Figure 5 indicates that to forecast the future financial burden of health care, it is necessary to factor in the age-specific costs of health care.

What, then, can be said about future changes in the curve of the relative burden of health-care costs over the next generation? Figure 6 presents three possibilities. The first is that there will be a proportional downward shift in the curve (Case A). This is the curve implied by changes in the average prevalence rate, which leads to a shift downwards at a constant average rate at all ages. The example in Figure 6 implies a decline in average prevalence rates of 1.2% a year, which locates all of the points in Case A at about two-thirds of the previous level. Had the figure assumed a decline of 1.5%, which is at the high end of current forecasts, the points on the Case A curve would all be located at about 60% of the original level.

Figure 6. How will the curve of relative disease burden shift?

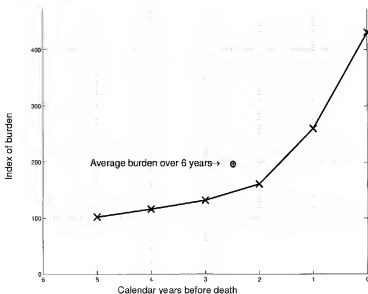


A second alternative – Case B in Figure 6 – is that the curve of disease burden by age will shift to the right. The Case B curve was constructed on the assumption that over the course of a generation, the average age of the onset of chronic conditions is delayed by about five years, an assumption supported by a number of epidemiological studies in the Netherlands, Britain, the United States and elsewhere. This forecast is based partly on the evidence that the average age of the onset of chronic disabilities has been rising since the start of the 20<sup>th</sup> century. It is also based on studies of the relative health-care costs in the years before death.

Figure 6 shows a third possibility, Case C, in which the curve of age-specific health costs twists. At ages 50-64, the curve shifts downwards, while at ages above 65 the curve rises. The downward shift before age 65 is due to a presumed acceleration of delay in the onset of chronic disease and an initially slower rate of deterioration. The sharper rise after age 65 is due partly to a diffusion of the most expensive interventions and partly to the assumption that the more effective interventions of the future will also be more expensive.

Figure 7 is standardised on the average costs of health care for all persons aged 65 or more in the US Medicare programme. It shows that five years before the year of death, the annual health cost is virtually the same as all annual Medicare costs per capita. By the second year before death the cost rises by about 60%, and in the year of death the annual cost is four times the average cost. Indeed, expenditure on persons during their last two years of life account for 40% of all Medicare expenditures. The pattern in Figure 7 has not changed significantly over the past two decades. The relative constancy of health-care costs by years before death supports Case B in Figure 6, since it implies that no matter how far to the right the health-care curve shifts, age-specific costs will eventually rise sharply as the proportion of persons who die in any given age category increases.

**Figure 7. Index of average annual health care by year before death**



## Forecasting trends in the demand for health-care services

So far, this chapter has focused purely on the economic burden of treatable chronic conditions. Figures 5 and 6 focus on the cost-adjusted supply of treatable conditions. The focus now shifts to the likely trend in the demand for health-care services by consumers. Table 2 presents the change in the structure of health-care consumption in the United States between 1875 and 1995; the trend in other OECD countries has been similar. The term “expanded consumption” takes account of the fact that as income has increased, consumers have preferred to take an increasing share of their real income in the form of leisure rather than purchase more commodities, as they might have done if they did not reduce their hours of work.

**Table 2. The long-term trend in the structure of expanded consumption and the implied income elasticities of several consumption categories**

Consumption class	Distribution of expanded consumption (%)		Long-term income elasticities
	1875	1995	
Food	49	5	0.2
Clothing	12	2	0.3
Shelter	14	8	0.7
Health care	1	9	1.6
Education	1	5	1.6
Other	6	7	1.1
Leisure	18	67	1.4

Table 2 has two notable features. One is the change in the share of income spent on food, clothing and shelter, which has declined from 75% of expanded consumption to just 12% over the 120-year period. The second is the share of income spent on health care, which has increased nine-fold, from 1% of expenditures to 9%. For purposes of forecasting, the most important element of Table 2 is the last column, which presents the long-term income elasticities for each category of expenditure. The income elasticity is defined as the percentage increase in expenditures on a given commodity that will occur with a 1% increase in income. The income elasticities for food and clothing are quite low, which means that the share of these items in total consumption will continue to decline. An income elasticity of 1 means that the share of a given item in total consumption will remain constant. Significantly, shelter – which includes most consumer durables – is closer to, but still below 1. On the other hand, the income elasticities for health care, education and leisure are all well above 1. The income elasticity of 1.6 means that income expenditures on health care in the United States are likely to rise from a current level of about 14% of GDP to about 21% in 2040.

Is that bad? Should such a development be avoided? Should governments seek to thwart consumer demand for health care services? Such a policy would be necessary only if OECD countries lacked the resources to provide that much health care. However, the growth in productivity for traditional commodities, including food, clothing, shelter and consumer durables, will release the resources required to provide expanded health care. In the United States a century ago, it took about 1 700 hours of work to purchase the annual food supply for a family. Today it requires just 260 hours. If agriculture productivity grows at just two-thirds of its recent rates, by 2040 a family's annual food supply may be purchased with about 160 hours of labour.



A recent study of the role of the change in the benefits and costs of health care, conducted by investigators at the National Bureau of Economic Research (NBER), concluded that the benefits of health-care services over the past 40 years have more than justified their costs. This suggests a fundamental repositioning of the public debate about medical care, from how governments can limit spending to how governments can obtain the most from health-care expenditures. NBER investigators have also suggested changing the methods of health-care financing so that consumer demand for increasingly effective services is not unnecessarily thwarted.

## *Chapter 4*

### **HEALTHY AGEING AND THE CHALLENGES OF NEW TECHNOLOGIES CAN OECD SOCIAL AND HEALTH-CARE SYSTEMS PROVIDE FOR THE FUTURE?**

*by*

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#### **Introduction**

Ageing is both an opportunity and a challenge (OECD, 1998). Increased life expectancy is a common feature of most countries today. At the same time, new technologies make ever more costly procedures available to health-care systems. These two phenomena illustrate how successfully modern societies have addressed the challenge of pushing back the boundaries of human life and of medical knowledge. However, they are both a blessing and a concern for policy makers in charge of ensuring the long-term sustainability of financing arrangements for health and long-term care.

Long-term sustainability has attracted increased attention in a period of slower growth in OECD countries. Research on health policy and on the policy implications of ageing has been stimulated by a growing awareness of the potential vulnerability of social arrangements that face fiscal pressures. At the same time, there is a better understanding of the implications of current demographic changes in developed countries. The situation has been most acutely felt in countries such as Japan which have experienced relatively slower growth or are experiencing ageing at a faster pace. As a result, OECD countries must face the question of what their social and health systems will be able to provide in future.

The answers to this question will influence the distribution of health and wealth, public finance arrangements and ultimately the social consensus upon which these societies are built. In the 1990s, the United States and some European countries experienced quite rapid growth, and as a result, the share of health expenditure in GDP stabilised near 8.2% between 1992 and 1999 for a group of 20 OECD countries (Australia, Austria, Canada, Denmark, Germany, Finland, France, Iceland,

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1. The author thanks the experts from national public and academic institutions who helped with the study and in particular Manfred Huber, of the OECD Secretariat, as well as Howard Oxley and Peter Scherer for useful discussions. Thanks also go to participants at the workshop on "Healthy Ageing and Biotechnology", at the Canadian Health Economics Research Association in May 2001, and at a seminar with the French Council of Economic Advisors and to Véronique Philippon for her research assistance. The views expressed here are the author's own and do not necessarily reflect those of the OECD or its member countries.

Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Spain, Switzerland, Turkey, the United Kingdom, the United States), a share significantly above that of earlier decades.

Contrary to what might be expected, most empirical results show that ageing, in itself, is not a strong driver of health-care costs. Even if these are apparently linked to age, and even if 40-50% of health-care expenditures are devoted to older persons, there is no link at the aggregate level between levels of spending and the relative demographic situation of societies. In addition, the concentration of health-care costs at the end of life biases data on the distribution of costs by age. In most countries, projections corrected for this mortality effect show that the impact of ageing, albeit real, does not by itself explain the structural pressures faced by health-care systems. The relationship is far more complex. Studies tend to show that differences in income, and supply-side and institutional variables, account for most of the differences in treatment patterns – and also in health-care costs – across countries, although cohorts and generation effects may also play a role over time.

Trends in long-term care systems are affected by trends in disability, de-institutionalisation, changing social models and policy-driven incentives. Recent OECD studies show that most countries have experienced reductions in disability and, to some extent, de-institutionalisation of their older population. This will have an impact on the number of older persons needing care in future but less impact in terms of public finances. However, if older persons are less disabled, they may still suffer from significant morbidity: reductions in disability may result from costly new health-care interventions.

As a result, developed societies need to provide better health and long-term care with limited resources, including constrained public finances. This requires assessing use of technologies and their improvement of health outcomes, in terms of their private and public benefits.

This chapter first briefly discusses the background, in terms of ageing and the role of technology. Second, it analyses the relation between ageing, health and expenditures on long-term care. It discusses the “naïve” ageing fallacy while taking into account the cost of dying and the dynamics of age-adjusted health expenditures. Third, it looks at the implications of long-term care and disability. Finally, it draws out the policy implications to point out the challenges faced by health and long-term care systems.

## **Background**

### ***Ageing and its policy implications***

While in itself ageing is already a policy issue, fertility, which is also important in the long run, has a limited impact on the social and economic implications of ageing in the next 20 to 30 years. The current demographic situation is largely the result of the decrease in mortality at higher ages in OECD countries. The decrease in mortality is observed even in the oldest age groups. As a long-term analysis shows (Fogel, 1994), this is largely the result of improved socio-economic conditions, mainly nutrition but also housing and sanitation, which have had a significant impact on the longevity of the population as a whole. While the role of health care is important, it is certainly not the only, or even the main, contributing factor in the general decrease in mortality.

Ageing certainly requires a shift in the policy focus, with a proper balance between expenditures on pensions, health and long-term care. A long-term perspective and a clear understanding of the fiscal implications of age-related expenditure are needed. Ageing also requires the development of longitudinal surveys to understand the interrelationships over time between health, wealth and the

demography. The bulk of current age-related resources is directed towards pensions, health and long-term care, but long-term care expenditures are often difficult to identify (Jacobzone, 1999). The challenge for policy is to devote an appropriate share of national income to pensions, to health and to long-term care while keeping the overall burden of age-related expenditure in line with national resources. In terms of long-term care, the needs of an older person may be different at the very end of life: there may be less need for income and more need for high-quality care. Policy discussions often focus on pensions, as the distribution of expenditure on pensions is more sensitive to age structure than the distribution of expenditure on health (Blanchet, 1994). However, in many countries, health and long-term care represent a significant challenge. The focus of this chapter is therefore on resources “in kind”, including health and long-term care, but the monetary dimension should not be forgotten.

### *The diffusion of new technologies*

Technology is the other, often hidden, side of the coin. In the policy debate, many analysts tend to attribute the rapid growth in health expenditures to ageing, whereas, in fact, it mainly results from the diffusion of new technologies. This often leads to biased judgements and ill-formulated policy debates, in which ageing is used to promote a “Doomsday” perspective. In fact, taking technology into account allows for a better understanding of what is really going on in health-care systems. The diffusion of medical technologies in the Western world today is highly dependent upon institutional and economic incentives in the US health-care system (Weisbrod, 1991). The invention of new technologies is affected by policies that foster relationships between academia, government-financed-research and property rights legislation, and the US health-care system gives very generous incentives in this area.

Once technologies are available, the patterns of diffusion within health-care systems are largely subject to supply-side economic incentives embedded in those systems, which are, in turn, related to the relative propensity of government and health-care systems to pay for those technologies. Recent OECD work on ageing-related diseases found that supply-side incentives play a key role in the availability and use of the costly technologies that in a sense give rise to the expenditures in modern health-care systems: MRIs, lasers, mammography machines, PTCA, catheterisation laboratories, etc. (Jacobzone *et al.*, 2002).

In medical trials, technologies are often evaluated under well-defined circumstances, with limited samples of the population, but they may later be used well beyond the appropriate range of application. Certain analysts have asked whether some technologies have not become ineffective through overuse (Phelps, 1994), as they may be used in situations other than those for which they were designed. The marginal cost effectiveness of medical interventions varies in different groups of the population, and many developed countries face decreasing marginal returns to medical technologies because of their widespread use. This may not harm patients and may produce marginal health benefits in terms of quality of life. However, this certainly harms patients’ purses, or at least those of their insurers, who will in return require higher premiums or taxes.

The managed-care revolution, which has transformed the US health-care system in recent years, has constrained the use of technologies under conditions of low marginal effectiveness. Emphasis should be placed on incentives to reduce the cost of treatment, keep people out of hospitals and institutions and reduce disability (*e.g.* Lichtenberg, 1996). There are however concerns that managed care may slow the pace of medical research (Hellerstein, 1998) or foster a different mix of research.

## From a static to a dynamic perspective on health and long-term care expenditures

### *The drivers of health-care costs*

Applying traditional macroeconomic techniques to the health field has shed some light on the drivers of health-care costs. Studies have found that ageing has a limited impact on trends in health expenditures and accounts for only a couple of percentage points of the total increase in these expenditures (Newhouse, 1992; L'Horty *et al.*, 1997; Gerdtham and Jönsson, 1992). Among other things, the increase in national income plays a key role, together with price effects; institutional variables that describe health-care systems, such as general practitioners acting as gate-keepers or overall prospective budgets, play a limited role. The challenge now facing health macroeconomics is the need to identify the source of more than 50% of the total increase in costs. Health economists have attributed this large residual to technology. For example, recent US work (Cutler *et al.*, 2000) has shown that the key factor has been the increase in the volume of the diffusion of technologies for heart attack patients.

**Table 1. Health expenditures and share of the population aged 65 and over**

Country	Percentage of GDP spent on health 1998 <sup>a</sup>	Ratio of health expenditure old/young <sup>a,c</sup>	Percentage of population over age 85 1998 <sup>d</sup>	Estimated percentage of GDP spent on health for the elderly <sup>b</sup>
United States	13.6	3.8 (1)	12.4	4.8
Germany	10.5	2.7 (2)	15.9	3.5
Switzerland	10.3	4 (3)	15.5	4.4
France	9.6	3 (3)	15.7	3.4
Canada	9.5	4.9 (2)	12.4	3.9
Sweden	8.4	2.8 (3)	17.7	3.2
Australia	8.3	4.0 (2)	12.1	2.9
New Zealand	8.1	4.3 (5)	11.8	2.9
Japan	7.6	4.9 (5)	16.2	3.7
Czech Republic	7.2	2.8 (5)	13.8	2.2
Spain	7.1	3.3 (4)	16.3	2.8
Finland	6.9	4 (3)	14.6	2.8
United Kingdom	6.7	3.9 (3)	15.7	2.8
Korea	5	2.4 (2)	6.5	0.7

Notes: a. Health expenditure for the population aged 65 over health expenditure for the population aged 0-64.

b. This share is a first stage estimate, using the existing ratio and applying it to the 1998 expenditure.

c. OECD Health Data.

d. UN population statistics.

(1) 1995; (2) 1994; (3) 1993; (4) 1998; (5) 1997.

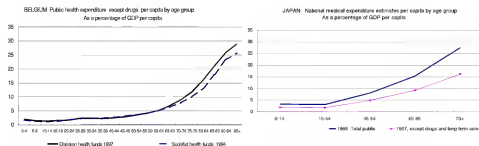
### *Ageing and health expenditure*

At first sight, health and ageing seem to be closely related in terms of health expenditures per capita and age. Recent evidence from OECD countries shows that health expenditure for people aged 65 or more is three to five times higher than for those aged 0-64 (Table 1). Older persons require more health services in all countries. In other words, an estimated 35% to 50% of health expenditure is

devoted to elderly persons. A “natural” conclusion is that ageing should have a significant impact on health expenditure. This seems to be demonstrated by the age profile of health expenditure.

Figures 1-5 present “age profiles” of health expenditure per capita by age group and as a percentage of GDP per capita. However, they should be interpreted with caution as they are often the results of empirical research based on a number of assumptions, particularly regarding the use of hospital services. Most of the profiles refer only to publicly financed services. Household surveys are needed to estimate the use of private services, and the corresponding monetary amounts are often difficult to estimate. In all countries for which such profiles are available, they show increases with age. In countries where the breakdown is available, women consume more health care than men in the middle age groups owing to pregnancy (see the New Zealand profile in Figures 5). In addition, health expenditure for the youngest age groups is also higher owing to expenditure at birth. Figure 1a shows the standard distribution by age for countries for which only a single year was available. The profiles in Figure 1b add a breakdown by public and private expenditures: in Australia, the relative share of public expenditure is similar for older and younger age groups. In Canada, the public share is high, although it declined slightly between 1980 and 1994, more so for the younger age groups. In the United States, where the data only include Medicaid, the public share is low for the younger age groups and higher for the older age groups.

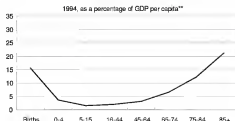
**Figure 1a. Health expenditure profiles by age groups**



Source: Clausse (1997) and Federal Plan Bureau.

Source: Ministry of Health and Welfare (1999).

**ENGLAND: Expenditure on hospital and community health services per capita by age group\***



\* Data cover only England.

\*\* GDP of the United Kingdom.

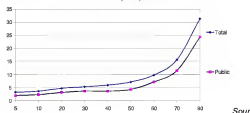
Source: Department of Health.

To obtain an accurate understanding of age-related implications, it is important to identify expenditures on long-term care. However, for most countries, long-term care is only included to a minimal extent in these expenditures. The data for Japan (Figure 1a) show the difference if long-term care and drugs are removed. However, the boundary between acute and long-term care is difficult to draw in Japan, as hospitals also provide long-term care. In most countries, in fact, it is difficult to disentangle health-care costs from long-term care costs. However, health and long-term care expenditures have different determinants, which are considered separately below.

Traditionally, health expenditure profiles are combined with population projections to project future health expenditures (Schneider and Guralnik, 1990; Franco and Munzi, 1997). Such projections exist for a number of countries and illustrate the future impact of ageing on health expenditures. These projections are not to be considered as “real numbers” but as a snapshot of the simple effects of demography, a superficial view of the relations of age to health expenditure.

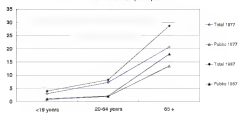
**Figure 1b. Health expenditure profiles by age groups with total, public and private breakdown**

**AUSTRALIA: Total and public health expenditure by age group, 1989-90**  
As a % of GDP per capita



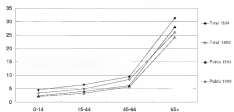
Source: Goss (1994).

**UNITED STATES: Total and public health expenditure (1977-87)**  
As a % of GDP per capita



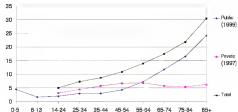
Source: Waldo et al. (1989).

**CANADA: Total and public health expenditure per capita (1980-94)**  
As a % of GDP per capita



Source: Health Canada (1997).

**ITALY: Total, public and private estimates of health expenditure per capita**  
As a percentage of GDP per capita



Source: ISAE, data for private expenditure correspond to the head of household, data under the age of 23 and above 90 are not statistically significant.

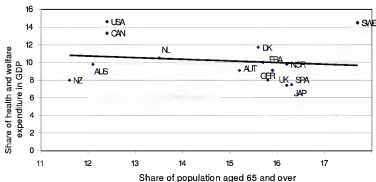
### **Beyond the naive fallacy**

The “Doomsday Prophecy”, which presents population ageing as a threat to health and social systems, is a naive fallacy. Demography is a secondary factor in explaining the overall increase in health expenditure. The key factors are use of technology and relative prices of medical inputs,

combined with the intensity of care at older ages. The extent to which formal long-term care is provided also plays a role.

At the aggregate level, there is no link between the share of the population age 65 or more and the relative level of health expenditure as a share of GDP (Figure 2). Economic and social incentives channel the impact of ageing through the health and welfare systems. Sweden, which has the highest share of its population aged 65 or more, spends relatively more on health and long-term care but not more than the United States, which has a much younger population. Yet Sweden is able to provide adequate coverage for health and long-term care and this delivers a positive message to OECD societies, as the ageing of its population did not lead to a collapse of the Swedish economy or its welfare system. Japan spends relatively less than other countries on health and long-term care and currently has a slightly larger share of its population aged 65 or more than some European countries.

**Figure 2. Health and welfare expenditure versus the share of the population aged 65 and over**



Source: AIHW (1997), *Older Australia at a Glance*, OECH Health Data 2000, OECD estimates. These data include health-care expenditure plus an estimate of formal expenditure on welfare and long-term care services.

The relationship between the share of the population aged 65 or more and health expenditure does not imply any causal link. An understanding of the complex long-term relationship between health, long-term care and ageing requires taking into account the supply-side and institutional characteristics of social and health systems. Ageing *per se* is not the key problem, but the extent to which technology is being used at older ages and whether it is cost-effective. In addition, the cost of dying needs to be taken into account.

### ***The impact of the cost of dying***

A second factor which mitigates the impact of ageing, is the concentration of health-care costs at the end of life. Failure to take this into account may lead to significant overestimation of future projections of health expenditure (Fuchs, 1984; Breyer, 1999). Health expenditure for older age groups is higher simply because a larger share of those groups is likely to die and therefore have high health expenditures. Although the findings may differ from country to country, it generally appears that in every country costs accumulate at the end of life.

Expenditures begin to increase slowly in the years prior to death (Lagergren and Batljan, 1999). More refined results show that the time remaining before death is important and that costs are highest



in the months immediately preceding death. However, the ratio of health expenditure for those approaching death to average health expenditure differs from country to country and across age groups. For example, in Denmark, this ratio is not very high (25% to 50% higher expenditures for decedents than for survivors). In addition, in several countries, expenditures for decedents in the middle-older age groups (60-75 years) tend to be higher than expenditure for those over 80. Scitovsky (1988) shows that the ratio was higher for individuals who were less impaired, in terms of activities of daily living/instrumental activities of daily living (ADL/IADL). This shows that towards the end of life money is spent on the patients who are likely to benefit most. Several studies confirm that younger decedents tend to have higher medical expenditures, while older decedents have lower medical expenditures but higher expenditures on nursing home, home care and supportive care (Lubitz *et al.*, 2001).

This has significant policy implications. As OECD societies are ageing, mortality rates in the older age groups will continue to fall. This will reduce the further rise of health expenditure and mitigate the impact of the demographic profile (Cutler and Sheiner, 1998; Zweifel, 1999).

### *A dynamic perspective on expenditure by age groups*

For many countries, age-expenditure profiles (Figure 3) are available for only one year. For a few countries for which time-series data are available, the data show an upward shift in the age-expenditure profile and illustrate the dynamics of health-care spending. In some countries the shift of expenditure is moderate whereas it is significantly more pronounced in others:

- ◆ Countries with a moderate shift:
  - In Finland, the shift between 1983 and 1990 seems to be relatively homogenous across age groups. Finland is a country with a fairly old population, and it has been able to contain the growth in its health-care expenditure expressed as a percentage of GDP.
  - In Canada, the shift is almost non-existent as health-care expenditure per capita increased only slightly between 1980 and 1985 and remained almost flat between 1985 and 1994, an era of cost-containment in the Canadian system.
- ◆ Countries with a more pronounced shift:
  - In France, the shift over 20 years<sup>2</sup> shows an increase in expenditures related to birth, as well as an increasing shift for the oldest age groups, although the data are limited to medical expenditure and exclude hospitals. Expenditure peaks for the 80-89 age group and is slightly lower for the oldest old. These shifts are due to more intensive follow-up for births and to more general medicalisation at older ages. Expenditures are lower for the oldest old as long-term care expenditure is not included in the data.
  - German data available over 18 years shows a clear shift for the older ages. Germany has experienced rapid growth in its health expenditures during the period that began just after the first oil shock.
  - The United States experienced an even more pronounced shift over the period 1963-87 (Cutler and Meara, 1999; Cutler *et al.*, 2000). The shift was more pronounced for the older age groups. More recent data compare 1995 and 1987, but with a different age

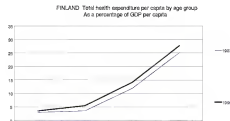
2. Similar but less pronounced trends would be observed for the period 1960-70 (Mizrahi *et al.*, 1974). However, the expenditure data from the 1960 survey were not fully comparable.

breakdown (Hodgson and Cohen, 1999). This confirms the further shift in the higher age groups between these two dates.

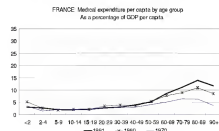
**Figure 3. Health expenditure profiles over time**



Source: National Health Expenditure in Canada (Policy and Consultation Branch, Health Canada) (Jan. 1998).



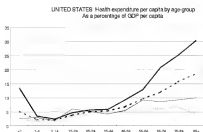
Source: Hakkinen (1996).



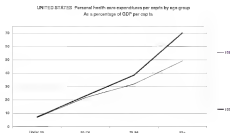
Source: National health surveys; Mizrahi and Mizrahi (1988; 1993); CREDES. Excludes hospitalisation.



\*West Germany only.  
Source: Deutscher Bundestag 13. Wahlperiode (October 1998).



Source: Cutler and Meara (1997)



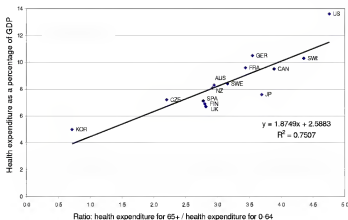
Source: Hodgson and Cohen (1999).

Detailed US studies have shown that most of the increase in expenditure at older ages is due to the more intensive use of technology (Fuchs, 1998). For example, the number of older persons in the United States receiving procedures such as angioplasty, coronary artery bypass graft, carotid endarterectomy or hip replacement increased three to ten-fold for the oldest age groups between 1987 and 1995 (Lubitz *et al.*, 2001). The impact of ageing is largely due to the use of more intensive

treatments and more expensive technologies. The United States is certainly the country where this phenomenon has been the most pronounced.

A standard way to illustrate this is to compare the “gradient” of the age spending curve across countries, with their relative propensity to spend on health care. When the ratio of health expenditure for those over 65 compared to those under 65 is plotted against health expenditure as a share of GDP, a clear correlation emerges. The countries which tend to spend most on health also tend to spend relatively more on health care for the elderly (Figure 4).

Figure 4. Health expenditure as a share of GDP and ratio of health expenditure

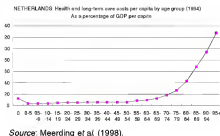
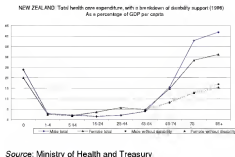
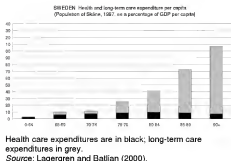


### Accounting for long-term care

The other dimension of health-related expenditure is long-term care (Figure 5). Long-term care plays a predominant role towards the end of life and needs to be considered separately from acute care. For example, in Australia in 1994, the bulk of the increase in health expenditure per person by age group was related to nursing home care. In New Zealand, the increase in expenditure over age 65 is clearly related to disability support. In the Netherlands, the age profile is much steeper than in other countries and culminates at a much higher level. This can only be due to the impact of long-term care (Meerding *et al.*, 1998). The situation is similar for Sweden. For both these countries, formally provided long-term care is more important than in the rest of the countries studied here.

Future trends in long-term care expenditure are likely to be influenced by trends in health and disability, by the relative availability of formal care and by the relative price of care. The availability of informal care is certainly being pressed by social changes and the increased participation of women in paid labour markets (Jensen and Jacobzone, 2000). In addition, the strong preference for independent living will be reinforced by the increased financial autonomy of older persons in OECD countries (OECD, 2000).

Figure 5. Health and long-term care expenditure profiles



The impact of trends in disability on health and long-term care expenditures have been debated in the literature, particularly since trends in disability in the United States have fallen continuously over the past 17 years (Manton, 2001). Although long-term care represents a very high level of expenditure at the end of life, it represents only modest expenditures at the macroeconomic level for most countries: between 1% of GDP in North America and continental Europe and 3% of GDP in northern Europe. In a previous study (Jacobzone *et al.*, 2000), future numbers of disabled older persons were projected under two assumptions:

- ◆ Constant rates of disability (static projection).
- ◆ Further changes in disability, factoring in recent changes.

This made it possible to disentangle the dynamic impact of trends in disability from pure demographic effects (Table 2). Reductions in disability have occurred mostly in the United States, Japan, France, and Germany and to a lesser extent in Canada and Sweden. The United Kingdom and the Netherlands did not exhibit any significant decline. Better health plays a significant role for the future health of the population but the impact is more moderate from the perspective of public finances, as disability is not the only factor to be taken into account. The bulk of resources is absorbed by care in institutions: trends in de-institutionalisation do not necessarily reflect underlying trends in disability, as they are driven more by policy incentives. Taking into account the trends in disability, the increase in expenditure remains modest in a number of countries. The United States is, in fact, the only country where these expenditures, as a share of GDP, would remain stable under an assumption of further reductions in severe disability.

**Table 2. Trends in the future numbers of disabled older persons and related publicly funded long-term care expenditure**

	Evolution of the total number of disabled older persons		Evolution of publicly financed long-term care as a share of GDP	
	Dynamic projection 2020/2000 (%)	Static projection 2020/2000 (%)	Dynamic projection 2020/2000 (%)	Static projection 2020/2000 (%)
Australia	+52.0	+58.1	+21.2	+58.4
Canada	+43.3	+61.4	+24.7	+47.6
France	+24.8	+42.6	+45.5	+50.9
Germany	-0.9	+17.6	+24.5	+37.2
Japan	+44.0	+73.9	+69.5	+101.8
Netherlands	N/A	+45.2	N/A	+48.9
Sweden	+5.9	+28.0	+8.3	+27.2
United States	+15.4	+38.3	-3.3	+21.1
United Kingdom	+11.3	+11.9	+15.9	+20.4

Note: Population aged 65 and over.

Source: Jacobzone *et al.* (2000).

## Policy implications

These results have significant policy implications (Jacobzone *et al.*, 2000):

- ◆ Are the trends in disability relevant for health policy as a whole?
- ◆ Do these trends have an impact on future health expenditure?
- ◆ Do the trends in disability reflect the performance of various health-care systems?

A number of analytical studies have been undertaken in the United States to understand the causes of reductions in disability. Research on long-term trends shows a significant reduction in the prevalence of respiratory conditions, ischaemic heart disease and joint and back problems. Reduced exposure to infectious disease early in life certainly played a role at the beginning of the century. (Costa, 1998). Research on more recent trends has shown the impact of education and related socio-economic factors (Freedman and Martin, 1999). These factors play a role, but are not amenable to health policy.

The most detailed recent work (McClellan and Yan, 2000) finds increasing morbidity among older persons, but this increase in the prevalence of disease is accompanied by less disability: older persons are "sicker" but less disabled. The diseases are more medicalised, but they allow patients a better quality of life. This is, in a sense, one of the achievements of modern medicine: it does not eliminate health risks, but it mitigates their impact and transforms them into chronic conditions which are manageable through treatment and medical follow-up. In turn, this means that declines in disability may, in fact, be very costly to achieve, since this reduction in morbidity through medical care needs to be financed.

Countries such as the United Kingdom, which use technology to a lesser extent, do not show the same trends. These trends are more pronounced in countries such as the United States or France which offer generous access to technology up to an advanced age. On the other hand, countries like the United Kingdom are experiencing difficulties with waiting times and the availability of certain

medical technologies. Whether this might have an impact on the health of older persons remains a hypothesis for future research.

### ***Back to technology and away from the Pasteurian paradigm***

This brings the discussion back to a better understanding of the true role of health-care systems. Modern health-care systems in many OECD countries have been built upon the Pasteurian paradigm of risk, infectious diseases and protection against sudden very high expenditure. However, modern diseases are highly likely to be present in old age, and are, for the most part, non-communicable. They often lead to continuous treatment and significant expenditures until the end of life. In a sense, health-care systems are increasingly furnishing quality of life at older ages, and to some extent extension of life at the oldest ages, rather than preventing mortality at a younger age. The latter function is still performed, but it is no longer the main function in terms of the relative share of current and future expenditures in OECD countries.

Here, technology and the supply of medical R&D are the key factor. Medical R&D is geared towards finding new medical treatments which may be more expensive and thus pose a challenge to policy makers. The advances of medicine now focus on increasing quality of life at older ages, with in a sense "public" and "private" benefits, and they are funded through a varying mix of public and private arrangements in OECD countries. If future pressures due to technology cannot be managed, this may affect the mix of public and private benefits in terms of the relative availability of some of these technologies, and the way that funding for less effective treatment is shared between the public and private purse.

### ***Understanding healthy ageing and maintaining the fragile equilibrium of health-care systems***

When examining the issue of healthy ageing, one needs to distinguish between disability, morbidity and quality of life. However, international agencies usually focus on "public" health indicators, which do not reflect "private" quality of life. Indicators such as life expectancy, cause of death, or even prevalence of disease, do not reflect "self-perceived" health or disability. In addition, further longitudinal data on the health of older persons is absolutely critical for obtaining a full understanding of the current trends across countries. These longitudinal data are needed to understand the relationships between technology, cost and quality of life. In most countries outside the United States, the available evidence remains limited. A number of countries have now implemented disability-related surveys. However, the number of countries with truly longitudinal data, which would allow assessing trends in health and understanding their causes nation-wide, remains limited.

The other important policy goal is to obtain appropriate control of the supply of technologies and their diffusion in health-care systems. Health-care systems need to avoid excessive restraint, which may be detrimental to patients' health, but they should also be aware of the limited marginal returns to some of the new technologies. Therefore, there is a very important role for health technology assessment as a tool in filtering the flow of new technologies that weigh on public finances. Technologies need to be screened, and only those yielding significant health-care improvements should be fully funded from the public purse. In addition, larger countries have a responsibility to take steps to influence the development of medical technology in a way that favours the development of more cost-effective technology. At present, providers lack the underlying incentives for developing cost-effective technologies. Also, the distribution of research across disease areas should reflect the burden of disease as well as the age-related and chronic diseases that now constitute a larger share of total health expenditures.

Health-care systems are likely to remain in a fragile economic equilibrium for the next decades. There will be constant pressure, as economic growth in most Western countries is not likely to achieve the levels of the 1950s and 1960s. Therefore, the need for priority setting and evidenced-based medical decision making will remain high on the political agenda. The policy dilemma can only be addressed through increased productivity in health-care systems, delivering value for money in improving quality of life.

However, the role, but also the limits, of a purely economic discussion of health-care systems should be recognised. Normative, but also positive, answers need to be found, building on social and political values. Policy makers have to acknowledge the role of ethics and the critical importance of reaching a social consensus on the amount of resources to be devoted to health care in a given society. Health-care systems are usually linked to levels of social consensus, and economists and health economists exhibit various degrees of consensus on a number of key health economics and health policy issues (Fuchs *et al.*, 1997). These levels of social consensus differ across OECD countries, and it is not likely that the same answers will be given to the same questions. Countries in which the population's preferences for medical care are fairly heterogeneous are likely to see a more limited role for public interventions, while countries where these preferences are more homogeneous are likely to require more extensive public involvement. The public, and implicitly the private, choices that will have to be made will ultimately reflect the various levels of social consensus as well as the various economic and institutional incentives.

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## *Chapter 5*

### **AGE AS A DRIVING FORCE OF HEALTH-CARE EXPENDITURE: SOME MACROECONOMIC EVIDENCE**

*by*

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Although there is a common perception that health-care expenditures increase with age, the correlation between the percentage of the population over 65 years of age and the percentage of GDP spent on health care is not very strong. Also, according to OECD data, there is not any clear correlation between pharmaceutical expenditures and the age of the population. Studies show that age itself does not seem to drive health-care costs. However, statistics from insurance companies in most countries indicate that cost per insured person rises with age, and this is the basis for the public perception that health-care expenditures rise with the age of the population.

Detailed studies have shown that the absolute number of people in a certain age group is important for permanent care and "prior to death" costs. According to studies by Professor P. Zweifel in Switzerland, health expenditures prior or near to death are about the same for those aged 30-40 and for those aged 60-70. In a country with a rising percentage of the population over 65, the expenditure curve is just shifted to the right (*i.e.* there is no increase in the number of "prior to death" or "near death" cases) and does not have a significant impact on the total amount of health-care costs. In fact, the latest studies give some indication of a reduction in the number of chronic diseases requiring permanent care owing to better therapies for diseases affecting persons between 40 and 65 years of age (*e.g.* osteoporosis, Parkinson's disease, stroke and cardiovascular diseases). In some European countries, it has been observed that "near to death" costs are lower at higher ages. For example, these costs for persons 67 years old were three times those for persons approaching the age of 90.

IMS data reveal a correlation between age and expenditures for drugs. In Japan, the share of prescription drug costs increases with age and provides evidence that supports the thesis that health-care costs rise with age. Data from Belgium, a typical European country, show a similar pattern. However, in Mexico and Brazil, countries with young populations and a lower life expectancy, the picture of the age-pharmaceutical expenditure relationship is very different and throws some doubt on the general assumptions made in countries with ageing populations.

Such statistics reveal the ambiguity of this issue. Recent studies give a broad overview of the drivers of health-care expenditures. Income is still the most important factor in health-care expenditures, not individual income, but GDP per capita or a country's total GDP. Another important factor is the nature of the health-care system, *i.e.* the incentives and disincentives driving the supply of and demand for health care. Most of the studies have found that a larger share of elderly persons has

*not* driven health expenditure. The classic OECD income/health-care expenditure graph still shows a close correlation between a country's level of welfare and wealth and its health-care expenditures.

Any discussion of health expenditure, therefore, should not focus on the percentage of GDP that should be spent on health care. It should focus on how to create incentives and disincentives for suppliers of health care and for patients, so that we eventually have an efficient use of the resources and mechanisms that allow individual patients to make the best use of health-care services.

## Chapter 6

### **SPEEDING ACCESS TO IMPORTANT NEW DRUGS: THE CHALLENGE OF DEVELOPING NEW PHARMACEUTICAL PRODUCTS FOR THE ELDERLY**

*by*

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**Tufts University, United States**

*"The Art of Medicine consists of  
amusing the Patient  
while Nature cures the Disease."*

Voltaire

We have certainly come a long way since the age of Voltaire. Today, advances in science and technology offer new opportunities to understand and treat diseases of the elderly. This chapter addresses some of the hurdles that stand between these new exciting technologies and a market product. What are the factors that influence the decision within pharmaceutical firms, biotechnology firms and other organisations to develop drugs for the elderly?

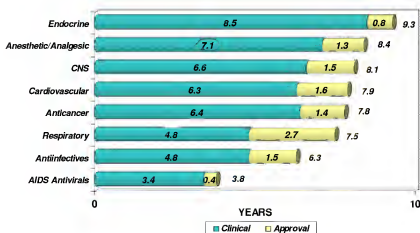
Economic factors assuredly play a role. An ageing population means that people are not only staying young longer but also staying old longer. The fact that elderly people tend to receive medicine-intensive chronic as opposed to acute treatment certainly provides important market incentives to develop drugs for the elderly. At the same time, there are political concerns about the rising cost of health care. There are further concerns – in the United States in particular – about the sizeable proportion of the elderly population that does not have any coverage for pharmaceutical products. This also influences the decision to develop these products.

The focus of this discussion will be on the collection, management, analysis and interpretation of data from clinical trials with elderly populations. An initial question relates to clinical trials that do not necessarily focus on diseases of the elderly but that could nonetheless include the elderly. Why, in the vast majority of these trials, are the elderly not included? Several factors contribute to their absence from these trials: co-morbidity in the elderly population; polypharmacy; compliance issues, especially for products that are being tested at an outpatient level; attrition – people drop out of trials simply because of ageing effects; unrelated illness and death; and, simply, the physiology of ageing which leads to effects that are different from those in a younger subject.

Some drugs are developed specifically for diseases of the elderly while others are developed for a broader population which also includes the elderly. However, the elderly are not a homogenous population. Elderly persons included in clinical trials are usually in their mid-60s and in relatively good health. However, once these drugs are approved, they may be used for people over 65 who have multiple diseases and take a number of other drugs.

Figure 1 presents diseases in an order corresponding to various therapeutic categories: cardiovascular, endocrine and non-steroidal anti-inflammatory-type products and cancer. This categorisation makes it a little easier to understand the implications in terms of the time to bring these products to market. Figure 1 presents data on a group of products approved in the United States between 1995 and 1999. Even though these products are approved in the United States, their clinical development may have taken place anywhere in the world. For each therapeutic area the bar shows clinical development time, *i.e.* the time from testing on humans to submission of a new drug application in the United States, and the time that the Food and Drug Administration (FDA) took to approve those products.

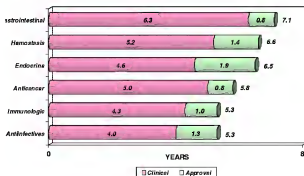
Figure 1. Mean clinical and approval phases for NCEs by therapeutic class, 1995-99



Source: Tufts Center for the Study of Drug Development (2000).

The figure highlights the fact that products with relatively easy end points, for example, anti-AIDS or anti-infective drugs, go through the process relatively quickly. In contrast, products for the elderly such as drugs for endocrine, central nervous system (CNS) and cardiovascular disorders as well as anaesthetic/analgesic drugs take longer. On average, it takes eight years or longer for these products to go from clinical testing to approval. Biopharmaceutical products (Figure 2) require a slightly different categorisation. But they also require a very long time for development.

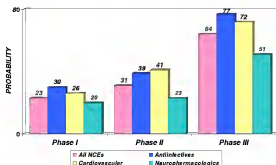
Figure 2. Mean clinical and approval phases for bio-pharmaceuticals by therapeutic class, 1995-99



Source: Reichert et al. (2000).

Developing products in these therapeutic areas is very risky. Figure 3 provides data on risk for all new products approved over a specific time period by category: anti-infective, cardiovascular and neuropharmacologic products. The figure shows the likelihood of drugs in these categories receiving approval in the United States. On average, of the products that begin Phase I clinical testing, between one in four and one in five eventually reach the marketplace. For anti-infectives the percentage is a great deal higher – 30% of those that begin clinical testing eventually receive market approval. For neuropharmacologics, on the other hand, only 20% eventually receive approval. For products in Phase II, percentages are slightly higher for more of the categories: 31% of all products move on to approval from Phase II; the other shares are (only) 23% in the neuropharmacologic category, 39% for anti-infectives and 41% for cardiovascular products.

Figure 3. Probability of approval for NCEs entering clinical phase of development



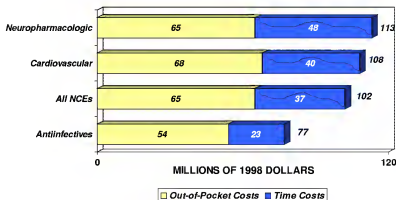
NCE = new chemical entity.  
Source: DiMasi et al. (1995).

The figures for Phase III show that about 64% eventually go on to receive approval. The anti-infectives that begin Phase III have a very high success rate with over three-quarters going on to approval. But some drugs late in their clinical testing (Phase III) still have a high probability of failure.

These products include the drugs for Alzheimer's disease and other drugs for CNS illnesses. The risks involved in developing such products are extraordinarily high.

Long periods of development and approval time combined with a high degree of risk means high costs. Taking all new chemical entities (NCEs), Figure 4 shows the clinical development costs for the four therapeutic classes defined above. The anti-infectives class, with short development times and a high degree of success, are the least expensive to develop, whereas cardiovascular and neuropharmacologic products are considerably more expensive to develop. The figures include the cost of failures in the development process as well as the opportunity costs lost in developing these products given the length of time involved.

Figure 4. Clinical development costs per approved NCE by therapeutic class



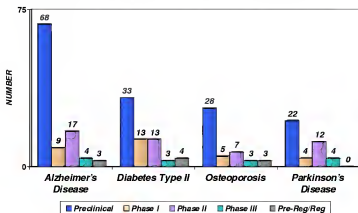
NCE = new chemical entity.  
Source: DiMasi *et al.* (1995)

While Figure 4 indicates costs incurred during clinical development, it does not include the pre-clinical phase of testing, which adds three or four years of testing and substantial expense. When these costs are taken into account, costs for each new chemical entity or new product to come to market average somewhere between USD 300 million and USD 500 million. The evidence for biopharmaceutical products is a roughly similar figure. However, this estimate only considers large firms with several products in the pipeline, not small entrepreneurial biotechnology firms with only one product under development.

Figure 5 shows the number of products presently in development for elderly patients. It highlights the fact that there are many products at the pre-clinical level. Of course, many will drop out before they get to clinical trial. At the clinical level, there is a relatively large number of products in almost every category in early clinical phases and very few in late clinical phases. This suggests that for some of the most important diseases of the elderly, very few products are going to reach the market in the short term.



Figure 5. Products in active development by indication for elderly patients



Source: Tufts Center for the Study of Drug Development (2000), PharmaProjects (September 2000).

The products at the pre-clinical level and in Phase I and Phase II are not expected to reach the market for at least another five to seven years. What government initiatives could serve as incentives to bring these products to market? In the United States, a geriatric labelling rule established about three years ago requires that products used by the elderly include labelling for the elderly. This means that the elderly had to be included in clinical trials for products that represent important therapeutic advances. Priority review and the fast-track process – which includes the Federal Drug Administration (FDA) in the United States and to some degree the European Agency for the Evaluation of Medical Products (EMA) – help ensure that clinical trials are designed to give manufacturers the results they seek. There has been some discussion about an extension of market exclusivity that would be modelled loosely on a paediatric initiative in place in the United States since 1997. This initiative gives manufacturers an additional six months of exclusivity for paediatric labelling or paediatric studies done on new drugs.

Clearly, then, developing drugs for elderly patients offers significant challenges that are not encountered when developing drugs for other populations. Long development times, risk and high costs characterise the search for drug treatments for all types of diseases, but especially for particular diseases of the elderly that tend to fall at the cardiovascular, CNS and endocrine end of the scale. Finally, government can play a role by encouraging the development of such drugs. Over the next few years, bringing such products to market, realising some of the exciting advances and scientific breakthroughs, will clearly require some assistance from government to help move things along.

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### III. SCIENTIFIC AND EPIDEMIOLOGICAL TRENDS

Current advances in biotechnology are helping scientists understand the basis of age-related diseases and suggesting possible preventive and therapeutic interventions. The genetic basis of multifactorial diseases, gene therapies, hormone replacement, stem-cell and organ transplants, and artificial tissues all provide hope that the diseases and conditions of later life can be prevented or controlled. Which among the approaches now in the laboratory are most likely to influence human health within 20 years? Which technologies are likely to have longer development times and why? This section takes both a technological and epidemiological approach. The technologies represent the potential supply of tools for age-related diseases, while the epidemiological studies indicate demand levels. Epidemiological studies give policy makers a map of where scientific efforts might be best directed (dementia, cardiovascular disease, cancers, and mobility and frailty) if governments are to attack the conditions and diseases that are most prevalent and most disabling in the elderly.

## *Chapter 7*

### **GENETICS AND GENOMICS OF AGEING: THEIR IMPACT ON UNDERSTANDING DIAGNOSTICS AND THERAPEUTICS**

*by*

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Though we like to think of ageing in positive terms, we are frequently forced to see ageing in terms of the increased risk of disease and the increased incidence of disorders that we would prefer to avoid. The relationship between age and disease poses a difficult problem for geneticists. Age-related conditions such as Alzheimer's disease, osteoporosis or diabetes run in families and clearly have genetic components. However, since these diseases arise in older individuals, transmission of these disorders is difficult to study because parents are not usually available and it will be many years before their children will or will not develop the condition. For this reason, it is difficult to apply the traditional methods of genetics, which follow inheritance of a phenomenon through many generations of a family. However, geneticists have been very innovative in finding ways around this problem. All the examples described in this chapter depend on the application of modern genetics and genomics, including results from the Human Genome Project.

#### **Early-onset diseases**

One way to overcome the problem of age-associated conditions is to look at early-onset forms of the disease. Alzheimer's disease (AD) offers a remarkable example of this approach. By examining families and populations in which AD began early, it is possible to look at generations within the lifetime of a single research project. Genes that give clues to pathogenesis and targets for therapeutic intervention have already been identified. Early-onset ovarian failure (menopause) is another such example. The mean age of menopause, which has been constant over many centuries and in many different cultures, is about 50 years of age. However, approximately 2% of women either never menstruate or go through a form of menopause in their late 20s or early 30s. This is a social problem in cultures where women tend to postpone childbearing until an age at which it is no longer possible for women with early-onset menopause to bear children. In some women, the cause of this disorder is genetic, and for such cases the Genome Project has helped to find the genes that may be involved by positional cloning. A number of genetic techniques indicate that some women with premature ovarian failure have a genetic abnormality somewhere on the third chromosome.

The human genome is made up of 3 billion base pairs divided up into 24 gigantic molecules, expressed on individual chromosomes. These molecules (chromosomes) are much too large to work with, but their clonal fragments, which are made up of a million base pairs, can be easily handled in

the laboratory. The Human Genome Project has made it possible to break down the entire human genome into overlapping clones, or small sections of DNA.

How are these clones used to find the gene involved in premature ovarian failure? In many of women with early-onset ovarian failure there is a break in the chromosome on chromosome 3, which interrupted a gene and separated the chromosome into two parts. One part of the chromosome became translocated to another chromosome in the genome. How can the Human Genome Project help? The Genome Project provides large molecules of DNA that cover the entire candidate region, and we sift through the DNA until we find the point at which the break occurs in the patients with premature ovarian failure. The DNA sequence is then available and we can look at the genes. Dr. Giuseppe Pilia and I have identified the interrupted gene in a number of these cases. It proves to be a gene which regulates the number of oocytes and follicles in women. When the gene is interrupted and its function compromised there are too few oocytes and follicles to support normal ovarian function.

Oocytes are surrounded by protective cells to form follicles. The number of oocytes increases early in embryonic life but most are lost later in life. Those that are left are incorporated into a follicle. At birth, a female baby will have all of the oocytes and follicles that she will ever have during life. Starting at puberty, with the onset of menstruation, the number of oocytes begins to decrease and reaches a low level at the end of the reproductive life span, *i.e.* at menopause. In women with premature ovarian failure, the formation of these follicles begins at a normal rate, but the rate of attrition is much increased, and at birth none may be left or too few to support the length of the normal reproductive life span.

In other words, to understand the age-related phenomenon of menopause and ultimately to do something about premature menopause, we must understand embryonic development. Insights in early life and in the embryo, mentioned by Professor Fogel (see Chapter 3), have an important bearing on what happens later in life. In fact, what happens in development is frequently crucial to the development of age-related conditions and disease. This has led to the notion that ageing, like any biological process, has genetic determinants that act early in human development. Ageing should be considered an extension of earlier development and depends greatly on processes that are initiated *in utero*.

This is an important change in our way of thinking about ageing. Ageing used to be viewed as a completely separate stage that took place after maturity. It is now increasingly clear that there is a continuum and that intervention to modify age-associated disorders may depend on understanding what happens earlier in life. The process by which cells or tissues lose their capacities or decrease in number during age-associated conditions is not usually considered until these reach the end-stage, for example in renal failure. However, if we know enough about development and know what cells and tissues need to survive, we may be able to preserve cell tissue or organ function or know how to regenerate them from stem cells.

In addition to positional cloning to hunt for disease genes, a second benefit of the Human Genome Project is an increasingly large catalogue of genes expressed by the mouse or human, which makes it possible to examine many genes simultaneously instead of one at a time. The National Institute on Aging (NIA), for one, is studying a set of 30 000 genes from the mouse, many of which are expressed only in early development. Dr. Minoru Ko and his group at the NIA looked at all the genes turned on in embryonic cells that are mortal and do not have an indefinite capacity to grow. They compared these genes with genes turned on in the cells that are immortal and give rise to the embryonic stem cells. In some cases, the genes are on in both the mortal and immortal cells. While 30 000 genes are a large fraction of the human genome, it is not all the genes. Advanced computer programmes now allow for analysis of the tremendous amount of data that are produced by such

experiments. For example, it is possible to analyse genes that are co-expressed, *i.e.* very high in expression at the time when some cells are becoming mortal but not expressed under a variety of other conditions. Thus, genes can be clustered by their capacity to be expressed together in a particular time or place and we can begin to discover which ones might be critically important in driving one process or another.

The Genome Project can also help in the analysis of complex traits. The analysis of the genetics of age-related conditions is difficult because many of these conditions are complex. If a disease is always caused by a change in the same gene, as is true for cystic fibrosis and many other paediatric diseases, it is only necessary to find the one gene in order to understand a great deal about the aetiology of the disease. However, in complex disorders such as diabetes, osteoporosis or Alzheimer's disease, many genes are involved: from five to 20 genes may contribute to different forms of the same disease. The problem is extremely complicated, because in one individual or family or population a variant form of one particular gene of this group may tip the balance and produce late-onset diabetes for example, but in another family or a different population a different gene may be critical. If the different families are lumped together, problems arise for the analysis.

Nevertheless, some of the factors involved are universal and can be investigated. The Genome Project gives not only the sequence of the entire genome, but the comparative sequence of individuals. It can then be asked: At what points does the DNA vary? Where are the changes in sequence that could lead to disease or disorder? Any two individuals except identical twins will differ at about 1 in 1 000 base positions in their DNA, so there is tremendous variation. But only a fraction of these, when they are in one form in a particular individual or family, seem to increase the risk of a certain disorder. "Increased risk", however, does not mean that these particular gene forms cause the disease. We are dealing here with genetic epidemiology; for example, with a different diet, the gene might not have this effect. All the variants can be tracked down.

A large number of the genetic variants being catalogued are called single nucleotide polymorphisms (SNPs). Of the 3 billion base pairs of DNA in the human genome, individuals will tend to have variations at about 3 million positions. Some will have one form of a gene, others a different form of the gene due to a polymorphism or variation of a single nucleotide. The positions at which all of these variants occur in the genome can now be localised, and some of these variations or polymorphisms are those that, when modified in a particular form, increase the risk of disease. The age of onset of Alzheimer's disease offers an example. A polymorphism of a particular blood protein, apolipoprotein E (ApoE) affects the risk of AD. There are three forms of ApoE: 2, 3 and 4. The risk of developing AD differs for each of these forms. Individuals with form 2 of ApoE have very little risk of an Alzheimer-like condition until a very advanced age. Individuals with form 3 present greater risk than those with form 2, but form 4 gives rise to much earlier onset. A single nucleotide polymorphism is sufficient, in the case of Alzheimer's disease, to confer considerable early-onset risk to individuals.

Dr. Alan Roses at Glaxo Wellcome studied the ApoE region of the genome, knowing that within the 2 million base pairs was a change that correlated with early-onset AD. Eventually, Roses found the exact point at which the ApoE-2-4 polymorphism was localised. Other attempts to localise important polymorphisms in the genome include the use of the SNP map to narrow the locus for psoriasis from an approximate position of over a million base pairs to a single gene. A locus for migraines which began as a very large region of some 6 million base pairs was linked to a 50 000 base pair region – again, a single gene – through SNP mapping. A locus for one gene that produces risk for late-onset diabetes started out as a large part of a chromosome 30 million base pairs long and came down to 10 000 to 20 000 bases, in other words, a single gene.

What are the implications of these advances in genetics and genomics? It has been medical practice since the 19<sup>th</sup> century to diagnose a disease and treat the dominant pathology. Genetics is now shifting the medical paradigm. In the past, breast cancer once detected was treated with surgery, chemotherapy or radiation. The new use of genetic risk factors, for example mutations in BRCA-1 or BRCA-2 genes, opens the possibility of averting the risk of future breast or ovarian cancers. Preventive measures such as ovariectomy for women who have completed childbearing or the use of tamoxifen or other agents in development may be able to block the progression toward cancer. For example, in the first prospective trial, women with the mutated genes that can lead to a lifetime risk of breast cancer of over 80% were supplied with tamoxifen. They showed a twofold reduction in the subsequent development of breast cancer. In other words, by identifying a risk, there is a chance of preventing the development of the disease rather than waiting for it to develop and then treating it. Colon cancer is another example. If it is known that individuals have mutations in a particular gene that confers risk for colon cancer, one can increase the frequency of colonoscopy and use new drugs that inhibit the development of polyps, the precursors of colon cancer.

It should be emphasised that the genetic substratum does not exist in a vacuum. There are important interactions between genes and the environment. Only caloric restriction has been shown to cause progressive prolongation of life and improvement of performance during ageing in a wide variety of organisms including primates. Studies of caloric restriction in mice showed that animals fed 40% fewer calories lived as much as 50% longer than mice fed *ad libitum*. These studies have now been extended to primates. A calorie-restricted monkey is a little bit smaller, but maintains its coat texture, retains its learning capacity and is more active than the monkey who eats *ad libitum*. The genetics are the same but the environment, in this case nutrition, is different. In another experiment, animals were fed *ad libitum* or had a diet low in calories. The two groups were then challenged with a drug that destroys a part of the hippocampus in the brain. The animals fed *ad libitum* lost hippocampal cells and had impaired learning compared to the animals that were given a calorically restricted diet. These retained the hippocampal cellular layer and had normal learning capacity. Thus, diet plays a very significant role. What are the genes that are altered by diet? What genes determine the capacity of caloric restriction to prolong life and decrease disease?

The view of ageing is shifting from a separate stage of life to an integrated extension of human development. What happens early in life is important, and knowing early determinants should help to intervene to maintain health throughout life. Genomics and genetics are also changing medical practice by identifying risk factors and shifting practice towards prevention instead of diagnosis and reactive therapy.

## *Chapter 8*

### **PHARMACOGENETICS AND AGE-RELATED DISEASES**

*by*

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Genetic advances affect the diagnosis and management of Mendelian genetic and complex diseases. Furthermore, pharmacogenetics influences the selection of the right medicine, the right dose for the right patient, in particular in the elderly population. In the next five to ten years we may see a new era of evidence- and genetics-based medicine leading to drug development, new genetic diagnostic tools and enhanced efficacy and tolerance of medicines. The Human Genome project (HUGO) and the SNP Consortium (TSC) are expected to accelerate significantly developments in these areas. It will be necessary to understand the ethical and legal implications of these anticipated changes.

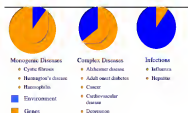
#### **Monogenic vs. complex diseases**

Most currently available gene-specific tests detect single-gene “Mendelian” (monogenic) disorders, such as cystic fibrosis, Huntington’s disease and various forms of muscular dystrophy. These tests detect the presence or absence of one or more gene mutations that lead to disease. In monogenic disorders, there is a strong causal relationship between the presence of mutation(s) and the occurrence of disease (for the relationship of genes and disease, see Figure 1). In the past 20 years, the causative gene mutations or the gene loci of several hundred human diseases have been identified. In many cases, this has led to the development and clinical use of diagnostic tests which allow diagnosis prior to clinical presentation of diseases and, where available, preventive therapy for some of the most devastating diseases. However, few effective interventions are capable of altering the progression of disease despite extensive international research efforts in the area of gene therapy.

A few examples of new therapeutic indications are based on a better understanding of disease mechanisms. For example, liver transplantation has proved effective in Familial Amyloidotic Polyneuropathy (FAP). FAP is a fatal autosomal dominant genetic disorder, affecting patients of all ages. The disease is due to the deposition of an abnormal protein in peripheral and autonomic nerves, the heart, and other tissues. FAP is rare in most parts of the world but is found in areas of Portugal, Japan, Scandinavia and the Mediterranean region. In the late 1980s, Dr. Saraiva and his collaborators identified the genetic mutations responsible and showed that the liver was the site of amyloid synthesis. This led to an effective therapy for the disease: liver transplantation.



Figure 1. Genes and disease



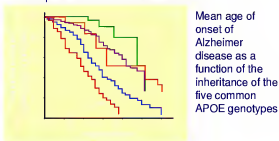
Source: Genetics Research, GlaxoSmithKline.

For a subtype of Friedreich's Ataxia (FA), an autosomal recessive, neurodegenerative disease, understanding the genetic basis of the disease has also led to a successful therapy, which makes use of a vitamin supplement. FA is characterised by progressive loss of co-ordination, dysarthria (speech disorder due to weakness or lack of co-ordination of speech muscles), sensory defects, paralysis of the limbs and cardiomyopathy. The disease-causing mutations in the vast majority of patients with FA affected the Frataxin gene on chromosome 9. However, a number of Mediterranean families have been identified with typical FA but without the Frataxin gene mutation. Most of these families were subsequently found to share *avitaminosis E*, owing to mutations in the gene encoding the alpha-tocopherol transport protein. This discovery permitted successful treatment of this subgroup of FA patients with vitamin E. Clearly the major challenge for new therapeutic approaches for genetic diseases in the years to come will be the ability to define and characterise accurately the clinical and genetic heterogeneity of monogenic diseases.

As opposed to the large number of monogenic diseases, each affecting a relatively small number of patients, complex diseases are fewer in number but affect many millions of people. The vast majority of complex diseases are "multifactorial", resulting from interactions among many environmental factors and disease susceptibility genes. Moreover, the pathogenesis of complex diseases usually results from interactions of several genes. An individual gene polymorphism is not sufficient to cause the disease but it is a risk factor for the disease. In several complex disorders, such as Alzheimer's disease or Parkinson's disease, a provisional diagnosis is made on the basis of clinical criteria, although we now know of many different genetic subtypes that may or may not share a common pathogenic mechanism. For example, in Alzheimer's disease, three gene mutations and one common susceptibility gene polymorphism are known (Figure 2). For this reason, a treatment for a common form of AD might not work for all patients with AD (Roses, 2000).

Figure 2. What is a susceptibility gene?

Example: APOE in Alzheimer disease

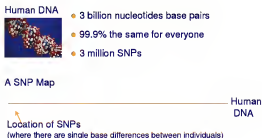


Source: Genetics Research, GlaxoSmithKline.

### SNP mapping

First reported in the early 1990s, single nucleotide polymorphisms (SNPs) are single-base differences in the DNA sequence that occur relatively frequently in the population. In the late 1990s, SNPs were identified as a potential genetic tool in molecular genetic studies of complex diseases and pharmacogenetics. The SNP Consortium – whose members include major pharmaceutical and information-processing companies, academic institutions and the Wellcome Trust – was formed to complete a high-density SNP map and place it in the public domain (Figure 3). The total number of SNPs in the human genome was initially estimated at 3 million, occurring approximately at the rate of 1 SNP per 1 000-1 500 base pairs. The goal of the Consortium was to complete a map of the 300 000 SNPs by the end of 2001. More recently, the total number of SNPs has been estimated to be 10-15 million. The number of SNPs identified is expected to exceed 1.5 million and the high-density map will contain approximately 1.1 million SNPs.

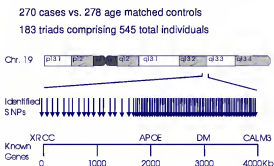
Figure 3. What is an SNP map?



Source: Genetics Research, GlaxoSmithKline.

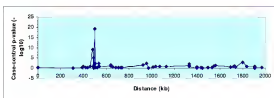
GlaxoWellcome scientists achieved the first proof of principle studying the SNP linkage disequilibrium (LD) for a susceptibility gene in Alzheimer's disease (Figure 4).<sup>3</sup> A high-density SNP map was constructed (Figure 5), spanning a 4 million base region around the APOE gene on chromosome 19 (Lai *et al.*, 1998).<sup>4</sup> A region of approximately 30-60 000 bases was identified, containing three SNPs with significant association to AD. This area included the APOE 4 polymorphism known to be a significant risk factor for AD. These findings showed that it was possible to detect SNPs in linkage disequilibrium with Alzheimer's disease.

**Figure 4. APOE/Alzheimer's disease proof of concept**



Source: Genetics Research, GlaxoSmithKline.

**Figure 5. SNP mapping of the APOE region**



Source: Genetics Research, GlaxoSmithKline.

- Linkage disequilibrium is often termed "allelic association". When alleles at two distinctive loci occur in gametes more frequently than expected, given the known allele frequencies and recombination fraction between the two loci, the alleles are said to be in linkage disequilibrium. Evidence for linkage disequilibrium can be helpful in mapping disease genes since it suggests that the two may be very close to one another.
- Certain alleles of the gene apolipoprotein E (Apo E) which encodes the protein apolipoprotein E have been reported to be associated with the development of Alzheimer's disease.

## Pharmacogenetics

Pharmacogenetics is the study of the DNA variations that control the responses of patients to medicines. The tools used in pharmacogenetics include differential gene expression studies, genetic data mining, proteomics and high-throughput proteomic screening, comparative genomics utilising transgenic animal models, *in situ* hybridisation and various techniques of tissue immunochemistry and histopathology.

There are many reports on the correlations between drug efficacy and DNA variations that affect a drug's mode of action. For example, polymorphisms in the gene encoding the cholesteryl ester transfer protein that are associated with changes in the mean lamina diameter suggest that patients have different responses to the drug Pravastatin (Kuivenhoven *et al.*, 1998). Moreover, Tan *et al.* (1997) showed that polymorphisms of the beta-2 Adrenoreceptor gene might correlate with efficacy of the agonist Formoterol. Anderson *et al.* (2000) demonstrated similar results for Salmeterol by showing that one phenotype associated with poor drug response is rare in Caucasians but not uncommon in African Americans. Figure 6 shows the modes of action of genes showing pharmacogenetic interactions.

**Figure 6. Pharmacogenetics: modes of action**

1. Gene - Drug pharmacokinetics interactions: biotransformation - excretion
  - P450(CYP)2D6
  - 2C9
  - 2C19
2. Gene - Drug pharmacokinetics interactions: transporters, receptors/targets
  - 5-HT receptor
  - D-4 receptor
  - MDR1
3. Gene - Drug interactions in disease etiopathogenesis:
  - Apolipoprotein E
  - CETP

Source: Genetics Research, GlaxoSmithKline.

Esteller *et al.* (2000) demonstrated that, in addition to genetic DNA variations, epigenetic (non-inherited) DNA changes might also affect drug response. Methylation of the promoter region of the MGMT gene, for example, was associated with partial or complete response of patients with gliomas to the nitrosurea alkylating agent carmustine. Methylation of the MGMT promoter predicted longer overall survival and time to progression of the disease. Methylation may exert its effect through transcriptional silencing of the gene affecting the expression of MGMT. Thus, patients with unmethylated MGMT promoter in the diseased tissues could be given an alternative medication, sparing them from the exposure to relatively toxic agents that for them would be of poor therapeutic efficacy.

With respect to drug safety, Lazarou *et al.* (1998) demonstrated the significant health-care implications and costs of iatrogenic adverse events in hospitalised patients. It is known that some variants of genes that encode drug-metabolising enzymes, receptors and drug transport systems affect the effective dose or adverse events caused by drugs. For example, in patients who undergo Isoniazid therapy for tuberculosis, peripheral neuropathy is a relatively common adverse event and leads to paralysis and loss of sensation in the limbs. It has recently been shown that the neuropathy is caused by mutations in the gene encoding the liver enzyme N acetyl-transferor NAT2. Meanwhile, susceptibility to becoming infected with tuberculosis in the first place may be associated with a

different genetic profile. Genotypes are correlated with the rapidity of activating drugs or of clearing them from the body. Patients can be classified as poor, normal or rapid metabolisers of individual drugs. Moreover, there are significant ethnic variations in the allelic frequencies of these types of genes.

### **Pharmacogenetics-enhanced drug development**

The current clinical trial model cannot identify rare adverse events occurring at an incidence of less than one in 1 000. For this reason, larger numbers of patients are required for Phase III trials, and this causes delays before patients have access to potentially beneficial medicines. Furthermore, the current clinical trial models usually provide no predictive information about whether individual patients will have positive results to the drug being tested, thus exposing many inadequately profiled Phase III patients to potentially significant health risks. New high-throughput SNP genotyping technologies may allow whole-genome SNP profiling. This could streamline drug development (*i.e.* pharmacogenetics-enhanced drug development) and the surveillance of drugs after they have been launched. By making possible a selection of patients in Phases II and III on the basis of their genetic profiles, pharmacogenetics should decrease the cost of drug development and increase the speed of entry of new drugs for better-targeted patients. In this way, patients with inappropriate “medicine-response profiles” will be excluded from trials for drugs of little or no benefit to them and/or of high risk of adverse events.

The introduction of a pharmacogenetics-enhanced surveillance system model for clinical trials may help to identify rare adverse events (AE). It may be possible to collect and store patient samples, such as blood spots on filter papers (Guthrie spots). As serious AEs are reported, DNA for those patients could be tested and compared with well-matched groups of patients who had received the drug without developing the same AE. AE-specific SNP profiles could then be determined, validated and linked to marketing approval (Roses, 2000). AE genetic profiles combined with efficacy profiles might produce a comprehensive medicine-response profile. Then, patients’ genes could be used to indicate whether a drug therapy would have high efficacy and low toxicity for them.

Ultimately, predictable efficacy, limited AE, reduction in serious complications and increased cost effectiveness will improve health-care delivery. Beneficial drugs will be available to patients at lower cost. It is important to recognise that we are, still, in the initial stages of pharmacogenetic research, and scientific data must be accumulated to support the introduction of such approaches in regulatory processes. However, it is important to start considering potential questions and barriers, conduct, evaluative models and proof of principle studies. Proactive regulatory guidelines are needed to facilitate the use of pharmacogenetics in timely and clinically appropriate ways in the next three to five years. The introduction of new medical technologies is driven by demand. As patients’ access to information on medical advances increases, their demands may soon become a powerful force to which public/regulatory authorities and the pharmaceutical industry will need to respond.

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## *Chapter 9*

### **EARLY DIAGNOSIS, IMMUNISATION, GENE AND CELL THERAPIES FOR ALZHEIMER'S DISEASE**

*by*

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In 1900, population was a pyramid, with many young persons at the base and a few elderly at the apex. At present, the pyramid has become a pillar, with almost equal numbers of young and old and a period of compressed mortality at the end of life. This transformation reflects the ageing of most populations in OECD countries.

With an ageing population there is more dementia. Dementia is expected to affect approximately 22 million individuals worldwide in 2000, 46 million by 2025 and 104 million by 2050. In 2000, two-thirds of the cases are in the more developed countries. By 2050, two-thirds of the cases will be in today's developing countries.

In the United States, the National Institute on Aging (NIA), created in 1974, is the major agency responsible for funding biomedical research on ageing. The NIA recognised from its inception that dementia would be the major health crisis of the 21<sup>st</sup> century and made a tactical decision to devote approximately half of its resources to study it. Initially, the NIA primarily funded individual investigators to study the biology of dementia. In 1984, the programme of the Alzheimer's Center was developed and called for longitudinal tracking of patients to carry out clinical pathological correlations and obtain well-characterised pathological material. In 1991, the Alzheimer's drug discovery groups and the Alzheimer's Disease (AD) Cooperative Study were set up to carry out clinical trials for agents that would not be developed by industry because these agents could not obtain patent protection.

We still do not know what causes AD. Currently, the most accepted hypothesis is that AD is caused by the aggregation of amyloid peptides to form amyloid oligomers. These oligomers deposit in the brain and cause nerve cell loss and biochemical defects, which in turn are responsible for the dementia syndrome. If this hypothesis is correct, many types of intervention are possible, including psychotropic agents for the dementia syndrome, cholinesterase inhibitors for the biochemical defect, mechanisms to prevent the loss of nerve cells and the use of anti-amyloid agents.

The agents developed so far are largely based on the observation, made in 1976, that there is a loss of cholinergic nerve cells (cells that release the neurotransmitter acetylcholine in AD). Cholinesterase inhibitor therapy produces a shift effect, so that if a treatment such as a cholinesterase inhibitor is applied to individuals with dementia who are getting worse over time, the individual will improve at first but will then track along a path parallel to the original slope of decline. Thus, such agents produce short-term benefits but do not alter the course of the disease.

The development of such agents is now fairly complete and several conclusions can be drawn about their use. First, the use of cholinergic agents, in particular cholinesterase inhibitors, produces measurable improvement on both cognitive test scores and on scales measuring the overall impression of caregivers and physicians. These agents may also have beneficial behavioural effects. Trials to date have been largely conducted in patients with mild to moderately severe disease. The magnitude of the effect of these agents, however, is fairly small, and the use of these agents does not appear to alter the underlying progression of neurodegeneration.

More recent pharmaco-economic analyses indicate the likelihood that use of the agents delays end points, such as placement in a nursing home, for a significant proportion of subjects. It is not yet clear whether the cost of the agents – drug plus monitoring – equals or exceeds the benefits of nursing home delay. Nevertheless, these drugs are widely used in virtually all OECD countries. Agents that slow or delay cognitive decline of patients with AD present a useful treatment strategy. If individuals can be identified early in the course of the disease and a treatment is applied so that the slope of decline decreases, a number of objectives would be achieved. First, an individual might be stabilised early in the course of the disease. Second, if the treatment works over a prolonged period of time, longer application of the treatment will yield greater benefits.

One trial attempting this strategy has been completed. Two agents: selegiline, a monoamine oxidase inhibitor, and alpha-tocopherol, an antioxidant better known as vitamin E, were used in a two-year study on 341 moderately impaired Alzheimer's patients. The end points chosen included death, institutionalisation, loss of two out of three basic activities of daily living, and progression from moderate to severe dementia based on the Clinical Dementia Rating Scale. The results indicated that both selegiline and vitamin E were independently associated with a greater time to end point. In this 730-day study, placebo patients reached end point after 440 days on average while patients on vitamin E reached end point after 670 days. This is approximately an eight-month delay in the time to the composite end point, or a one-third reduction in end points. The use of vitamin E was also associated with a significant delay in the time to institutionalisation and less deterioration in activities of daily living. However, in the standard neuropsychological tests, used to measure cognition, there was no obvious effect. Thus, the precise mechanism by which the effect occurred is not entirely clear. While there were clear effects on both basic and instrumental activities of daily living, which suggested a cognitive effect, instruments that test cognition could not confirm this. As a consequence of this study, at least in the United States, most individuals with AD are placed on both vitamin E and a cholinesterase inhibitor. We currently estimate that about 1 million Alzheimer's patients are on vitamin E and almost 700 000 on cholinesterase inhibitors. In Europe, most patients are treated with cholinesterase inhibitors and fewer with vitamin E.

There are also individuals with a syndrome called mild cognitive impairment (MCI). In general, these are people who present a memory complaint. When they are evaluated in a clinic they have a memory impairment that is characterised by problems with delayed recall. They can learn a list of words fairly well, but after 20 or 30 minutes they have difficulty recalling the list and perform at a level well below what would be expected of a person of the patient's age and education. They have normal general cognitive function, normal activities of daily living and clearly do not meet current criteria for AD, since they have an isolated memory impairment. Nonetheless, longitudinal studies show that these individuals will go on to develop AD at a very high rate. In a study from the Mayo Clinic, such individuals developed AD at a rate of 12% a year. In a similar analysis involving 700 patients from the Alzheimer Centers in the United States, the rate of conversion to AD was approximately 15% a year for a cumulative incidence of 45% at the end of three years. As a consequence of the high risk of developing AD, a randomised blinded study has been started with this patient population, and patients are treated with vitamin E, Donepezil (a cholinesterase inhibitor) or a placebo to try and prevent conversion to AD.



What effect might these treatments have on the number of individuals with AD? If the appearance of AD can be delayed by only one year, in 2007 there will be approximately 220 000 fewer cases. With more effective therapies, the delaying strategy will have greater impact. If AD were delayed by just five years, there would be 1.1 to 1.2 million fewer cases of AD in the United States. This is a very important public health approach to the disease process. Successful treatment would also translate into economic savings. In 2007, a one-year delay in developing AD in the United States would result in approximately a USD 9 billion savings in health-care costs. With a five-year delay, the savings would be USD 47 billion. Clearly, as the prevalence of AD increases in coming years, the savings become commensurately larger.

It has long been known that cholinergic cells are dependent on nerve growth factor, which is a potent neurotrophic agent for cholinergic cells. It increases cholinergic cell size and functioning in animals with damaged cholinergic systems or cholinergic loss due to ageing. It is known that cholinergic neurons degenerate in AD, and therefore it may be useful to consider administering nerve growth factor to patients with AD.

Rats with lesions in their cholinergic system have difficulty finding a hidden platform using a spatial memory task called the Morris water maze, in which a rat must find a platform submerged below the surface of the water using spatial cues within the room. A normal rat learns this task very well. A lesioned rat that receives a graft of cells that produce nerve growth factor in the cholinergic basal forebrain finds the platform almost as well as normal unlesioned rats.

Ageing primates also show an apparent loss of cholinergic cells in their basal forebrain compared to those of young primates. In aged primates, the number of cholinergic cells decreases by about one-half. But if an aged primate receives a graft of cells containing nerve growth factor, the number of cholinergic cells returns almost to normal.

We have initiated a gene therapy trial in which individuals undergo skin biopsies. Fibroblasts from these biopsies are grown in cell culture, and the gene for nerve growth factor is introduced into these fibroblasts using a viral vector. These fibroblasts are grafted back into the nucleus basalis in the brain of patients with AD. This is a very early safety trial, but it is also the first gene therapy trial that has been proposed and is carried out in patients with AD.

One hypothesis is that AD can be treated as "brain amyloidosis". If so, inhibitors of either beta or gamma secretase, the enzymes that generate amyloid from its precursor molecule, could be used to prevent amyloid from forming and thus prevent AD. An attempt could also be made to decrease fibril formation, enhance  $\alpha$ -beta clearance, or vaccinate to develop antibodies against amyloid to help in its removal. A process of vaccination to develop antibodies against amyloid was recently developed. The technique both prevents the deposition of amyloid if administered to young animals and appears to remove amyloid deposits from older animals. This technology has already moved very rapidly; the vaccination procedure is in human clinical trials, first in the United States and now in the United Kingdom.

The prevalence of AD rises very rapidly with age. While it may not be possible entirely to prevent the disease, an alternative may be to delay the age of onset. By merely shifting the age of onset by five years, since prevalence doubles with every five-year epoch, the prevalence in one generation would be halved. If it were shifted by ten years it would be halved again, decreasing the prevalence by 75%. From the public health perspective, this would clearly be the most efficient way of treating the disease. There are already a number of primary prevention trials based on a variety of hypotheses designed to delay the onset of AD. Two trials are testing the effects of oestrogen, another

is testing the effects of ginkgo, and yet another the effect of non-steroidal anti-inflammatory agents on preventing AD in normal populations.

This chapter concludes with three comments. First, when the author entered this field about 25 years ago, the answer to an AD patient's family question about the existence of therapies was "no". This has changed dramatically since 1993, with an increasing number of therapies becoming available and giving hope to patients and their families. These treatments are also extremely important for society because the costs of AD are enormous. Second, governments should be encouraged to embark on additional research. Looking at the total cost of health-related care and research in the United States, only about 1% is spent on AD. That is a disproportionately small amount. Third, it is important to know whether therapies work. They must be tested in randomised controlled clinical trials, the only way to reach valid conclusions. Using this approach, it will be possible to have some confidence that these are the kinds of therapies that it is worth paying to develop.

## Chapter 10

### NEURODEGENERATION IN PARKINSON'S DISEASE

by

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Parkinson's disease (PD) has received attention recently owing to the fact that some well-known persons suffer from the disorder, among them Pope John Paul II, Muhammad Ali and Michael J. Fox. Epidemiological data indicate that its prevalence is between 30 and 300 per 100 000 population. With the ageing of the population, prevalence is predicted to increase by 3% a year. It is estimated that by 2040 the total number of patients with Parkinson's disease will increase by a factor of four. The disease is diagnosed in 65% of cases and 56% are being treated.

The clinical manifestations of PD include slowness of movement, stiffness, tremor and impaired postural reflexes, but early in the disease the diagnosis may not be obvious. The course of the disease is fairly variable and unpredictable with factors such as age, the speed of the degenerative process, and drugs and treatment influencing the rate of progression.

Genetic and environmental factors are thought to contribute to Parkinson's disease. In PD, dopaminergic spiny neurons in the *substantia nigra pars compacta* degenerate slowly and cease to send their input, the transmitter dopamine, to the striatum. This puts the system out of balance owing to a lack of dopamine and ultimately leads to increased inhibitory input to the motor cortex, the motor control region of the brain. A pathological hallmark of the disease is the appearance of proteinaceous inclusions in the degenerating neurons, the so-called Lewy bodies associated with the disease.

Currently available treatment is mainly symptomatic and aimed at enhancement of the dopamine tone. The precursor to dopamine, levodopa or L-Dopa, can cross the blood-brain barrier although dopamine cannot. Levodopa is given alone or with COMT inhibitors,<sup>5</sup> which increase the amount of levodopa that reaches the brain by inhibiting its metabolism in the periphery, in an effort to replace the striatal dopamine deficiency. Another therapy is the application of dopamine agonists that directly stimulate the dopamine receptors in the striatum.

There are limitations to symptomatic therapy, however. Although patients often see an improvement after initial treatment, the degeneration of neurons in the *substantia nigra* is unaffected by the treatment. Very often increased motor disability occurs and, late in the course of the disease, patients develop Parkinsonian dementia. To reduce motor disability, alternative therapeutic approaches

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5. Catechol-O-methyltransferase (COMT) is one of the main enzymes responsible for the metabolism of levodopa, dopamine and other catecholamines (adrenaline and noradrenaline).

include neurosurgery. Pallidotomy can inhibit the over-functioning nuclei involved in motor control. Deep brain electrical stimulation can compensate for the missing input from the *substantia nigra*.

Other therapeutic approaches include cell therapy. The observed degeneration of the affected neuron population is confined to the *substantia nigra*. Initially, cell therapy involved the transplantation of autologous cells from the adrenal medulla gland, which is of neurological origin, to the *substantia nigra*. Human foetal mesencephalic cells have also been transplanted to replace the missing dopaminergic output of the *substantia nigra* cells. However, six to seven foetuses are required to obtain enough material for successful grafting. In addition, genetically engineered human fibroblasts and dopamine-producing cells that have been encapsulated to avoid any immunogenic stimuli have been applied in patients. None of these therapies, however, has ultimately proved to be successful on a large scale. Nevertheless, they have shown that surgical or stereotactic manipulation is feasible and accepted.

To treat PD effectively, degeneration of the dopaminergic neurons in the *substantia nigra pars compacta* must be prevented. The degeneration is thought to be due in part to an increased susceptibility of dopaminergic neurons to oxidative stress from free radicals. A specific defect in mitochondrial complex I occurs in 40% of the mitochondria in PD, which leads through the energy depletion of dopaminergic cells to death via apoptotic mechanisms. A variety of neuroprotective therapy approaches are under clinical trials, including the use of anti-oxidants or anti-apoptotic approaches.

The potential impact of biotechnology on emerging therapeutic advancements is considerable (see box). One possible approach is virus-mediated gene therapy. It makes possible the direct delivery of genes whose products protect the affected neurons, restore lost functions and promote trophic activity. The biggest problems with gene therapy, however, are accessing the target cell population, ensuring the efficacy of the gene transfer, the duration of the introduced genes *in situ* and the safety of the procedure. As an alternative, target cells from the patient could be manipulated *ex vivo* and then re-implanted.

#### How biotechnology contributes to the modification of Parkinson's disease

Direct therapy	Advances in safe gene delivery systems translate into successful therapies.
Genetic analysis	Discovery of causal genes and risk factors.
Pathological mechanisms	Efficient investigation and validation of underlying disease mechanisms.
Model generation	Integration of the above with transgenic technologies.
Drug discovery	Miniaturisation and increase of throughput translate above into drug discovery.
Diagnosis	Improved imaging technologies increase time and reliability.

Today, lentiviral vectors are favoured for the transfer of neuroregenerative or protective genes into the nervous system. These vectors, derived from the human immunodeficiency virus, have been modified so that all elements except those needed for viral replication have been removed. These vectors can effectively integrate genes into non-dividing cells without evoking an immune response. This form of therapy was reported to be successful in delivering a neurotrophic factor derived from glial cells into nigral striatal neurons of monkeys treated with a neurotoxin that selectively kills dopaminergic neurons. It was demonstrated that the therapy increased the number of surviving dopaminergic cells and, more importantly, resulted in functional recovery of least several months.

Two findings have stimulated consideration of *ex vivo* cell therapy. The first is the discovery of a specific survival factor, the *Nurr1* gene, for dopaminergic neurons in the developing brain. When the *Nurr1* gene product is absent, the development of dopaminergic neurons stops and those neurons die. Mice lacking the *Nurr1* gene show an increased sensitivity to dopaminergic toxins. The second finding is the discovery of multipotent stem cells in the target organs. The Ernest Arenas Group at the Karolinska Institute in Sweden has isolated stem cells from rat cerebellum and has propagated and transformed *Nurr1*. In the presence of the correct factors, these stem cells differentiate *in vitro* into dopaminergic cells. It is hoped that these cells can be re-implanted into the areas of cell loss in PD patients. However, the key to the success of this approach is the availability of human stem cells.

Biotechnology is also important in understanding human genetics. Several genes causing familial PD have been identified. The *Parkin* gene, for one, was originally identified in juvenile PD. This gene product was found to place ubiquitin residues on other proteins. Ubiquitination targets misfolded proteins for removal. Malfunction of this system can affect protein clearance and lead to an accumulation of malformed proteins which ultimately damages neurons. This possibility is of interest as PD has been shown to be associated with deposits of alpha-synuclein, the main constituent of the Lewy bodies, the pathological hallmark of the disease. Furthermore, when the alpha-synuclein gene is introduced into animals, a progressive motor decline develops. The pathology seen in the brains of such transgenic mice is very similar to that seen in patients with PD.

In conclusion, biotechnology can contribute to developing new disease-modifying therapies in PD using gene delivery systems to rescue dying neurons. Just as important, genetic analysis of PD can elucidate the pathogenic mechanisms of PD. Such findings will allow the development of animal models of the disease, which are essential to understanding the disease process and ultimately the selection of genes that can be introduced by gene therapy. Finally, the need for advances in imaging technologies should be mentioned, as they are important for measuring disease progression and therapeutic effect.

## Chapter 11

### VASCULAR GENE THERAPY: IMPLICATIONS FOR FUTURE TREATMENT OF CARDIOVASCULAR DISEASE

by

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This chapter focuses on how new revolutions in gene therapy may translate into new opportunities for effective clinical practice and on the major barriers to be overcome before gene therapy for various cardiovascular diseases enters clinical practice.

Statistics published in 1997 by the American Heart Association<sup>6</sup> identified the variety of cardiovascular diseases that affect the ageing population in OECD and other countries. In certain countries, such as the Russian Federation, other former Eastern bloc countries, the United Kingdom and Finland, total cardiovascular deaths account for up to 45% of total deaths. This demonstrates the extent and diversity of cardiovascular disease and the inadequacy of current treatment.

Environmental factors contribute significantly to the development of atherosclerosis and coronary heart disease, while other cardiovascular diseases have strong genetic influences. Hypertension is a classic example. Based on 1997 statistics, over 50 million Americans have high blood pressure. Although high blood pressure *per se* is not a major cause of death, it predisposes individuals to cardiovascular risks or stroke. In 90% of cases of hypertension, the aetiology is unknown. Complex genes regulate human blood pressure, and research is needed to identify and characterise the genes involved in predisposing individuals to hypertension. Many years of study will be required before new drug- or gene-based medicines are available that will target the genes that lead to hypertension. Stroke, which is responsible for 17% of deaths, is also relatively poorly treated owing to the need to administer therapeutics within two to three hours following stroke and the lack of basic understanding of the mechanisms involved in neuronal damage following the insult.

What are the fundamental requirements for developing gene therapies for vascular diseases that affect the ageing population? First and foremost, it is necessary to target diseases for which no effective pharmacological therapies exist at present. Second, the targets should be diseases whose molecular and cellular mechanisms have been clearly defined. This is particularly important for gene therapy, as unregulated overexpression of certain genes may have deleterious effects *in vivo*. Third, a prerequisite for effective therapy is adequate access to the diseased tissue in order to deliver the gene-based therapy, in other words the ability to target the tissue.

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6. [www.americanheart.org/catalog/Scientific\\_catpage70.html](http://www.americanheart.org/catalog/Scientific_catpage70.html)

Vascular diseases that are appropriate for gene therapy include acute disorders such as failure of coronary artery bypass grafts (CABG) and post-angioplasty restenosis, peripheral ischaemia, myocardial ischaemia and heart failure. Some investigators have even proposed gene-based therapies for complex, chronic progressive vascular diseases such as hypertension and atherosclerosis. Although it may seem ambitious to envisage eventual gene-based strategies for the long-term alleviation of high blood pressure or high blood lipids, recent developments in long-term gene expression have been encouraging.

Thus, based on the lack of pharmacological therapies for a number of diseases and the prevalence of cardiovascular disease in society in general, gene therapy may represent an unprecedented opportunity to treat or cure a vast array of clinical cardiovascular complaints. At present, the following diseases appear attractive candidates for gene therapy.

### **Myocardial and critical limb ischaemia**

Angiogenic growth factors, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and hepatocyte growth factor (HGF) have the ability to promote new blood vessel formation and hence have the potential to increase blood flow to ischaemic tissue. Patients with severe myocardial ischaemia or peripheral ischaemia have been recruited for a clinical gene therapy trial involving the local delivery of the VEGF gene to the ischaemic myocardium. Evidence in human patients using plasmid-based VEGF gene transfer directly into the myocardium (Losordo *et al.*, 1998) and intramuscularly for peripheral ischaemia (Baumgartner *et al.*, 1998) suggests that clinical benefit in patients may be obtainable. However, because VEGF is a potent angiogenic growth factor, its use must be carefully regulated as its overexpression can promote tumourigenesis (Lee *et al.*, 2000) and the progression of atherosclerotic lesions (Celletti *et al.*, 2000).

### **Hypertension**

Recent publications (Phillips, 1999) have suggested using the genes that code for inhibitors of the renin-angiotensin system in the therapy of hypertension. Angiotensin II type 1-receptor antagonists are pharmacological inhibitors of the action of angiotensin II in humans and are used as primary therapy to reduce high blood pressure but they require daily administration. Gene therapy using delivery vectors that provide sustained, long-term overexpression of genes (or antisense) to modulate blood pressure has been proposed as an alternative to conventional drug therapy. The principal advantage of gene therapy is that only a single dose is required for effective long-term reduction of high blood pressure.

### **Atherosclerosis**

Atherosclerosis is a life-threatening disorder that precipitates subsequent cardiovascular events and is very prevalent in Western society. Unfortunately, atherosclerotic lesions develop over decades, often beginning in the second decade of life and are thus difficult to treat. The group of drugs referred to as statins lower plasma cholesterol and reduce overall cardiovascular risk by 30%. Recent studies in animal models suggest that gene therapy of atherosclerosis may become a useful form of therapy. Three studies using different genes to treat atherosclerotic mice showed reductions in plasma lipids and the size of atherosclerotic lesions following single-dose treatments with viral vectors (Rouis *et al.*, 1999; Desrumont *et al.*, 2000; Oka *et al.*, 2001). Gene therapy may not just prevent the progression of atherosclerotic lesions but also induce their regression. The future success of this approach depends on greater knowledge of the molecular basis of atherosclerosis as well as the development of gene delivery vectors that provide long-term benefits.

## Angioplasty restenosis

Balloon angioplasty is a procedure used to restore efficient blood flow through an artery obstructed by atherosclerosis. Multiple inflations of a balloon catheter at the point of narrowing of the artery usually re-establish blood flow. However, restenosis, the re-occlusion of the artery, frequently occurs in the days, weeks or months after the procedure. Drug therapy has been largely ineffective in preventing restenosis. For this reason gene therapy using vectors, liposomes or viruses to deliver the gene of interest to the site of arterial occlusion at the time of angioplasty is under study. A number of genes, including nitric oxide synthase (NOS) (Janssens *et al.*, 1998), tissue inhibitor of metalloproteinases (TIMPs) (Dollery *et al.*, 1999) and cell cycle inhibitors have been proposed as candidates (Ohno *et al.*, 1994) for this local application of gene therapy.

## Vein graft failure

Coronary artery grafts with autologous veins is another means of re-establishing blood flow around arterial obstructions. However, as with restenosis following balloon angioplasty, obstructions within the grafted vein occur at a rate approaching 50%. Early graft failure is usually due to acute thrombosis, while late graft failure results from a proliferation of endothelial cells with superimposed atherosclerosis. Despite therapy with lipid-lowering drugs, graft failure remains a significant clinical problem. Gene therapy appears to offer particular advantages in this situation as the target tissue, the vein graft, can be manipulated prior to its grafting. Thus, safe and efficient genetic manipulation of the graft can be performed *ex vivo*. Furthermore, the mechanisms that lead to graft failure, the migration and proliferation of vascular smooth muscle cells, have been characterised. These mechanisms are principal targets for gene therapy, which has been shown to be effective in animal models and, in the case of E2F decoy oligonucleotides, in human trials (George *et al.*, 2000; Mann *et al.*, 1999). Results from a large trial of such gene therapies are eagerly awaited (Mann *et al.*, 1999).

## Conclusion

The studies discussed above use non-viral or viral-based gene delivery, either locally to the heart or the blood vessels, or systemically. Unfortunately, many of these delivery vectors are not efficient in targeting either the myocytes of the heart or the endothelial or vascular smooth muscle cells of the blood vessel. Viral vectors, such as adenoviruses and adeno-associated viruses are efficient at delivering the gene of interest *in vivo*, but these viruses also enter the liver and spleen as they lack a tropism for the diseased tissues and organs such as the blood vessel, heart, lungs, or the kidney. This lack of targeting leads to virus-induced toxicity, which has limited the use of such gene transfer vectors to local or topical application of the vector in angioplasty, vein grafting or myocardial disease. Even when these viral vectors are delivered to specific sites *in vivo*, the high concentration of the viral vector frequently leads to systemic dissemination of vectors that may evoke serious side effects. For this reason, clinical application of gene therapy depends on enhancing target-specific and disease-specific gene delivery systems. This should be possible through the genetic modification of viral vectors to prevent expression of proteins responsible for binding to non-target cells and the incorporation of genes that cause specific binding to target cells *in vivo*. While non-viral vectors are generally less efficient than viruses, improved targeting may not only enhance efficiency but also allow selectivity. The success of gene therapy will depend largely on improving gene vectors so that *in vivo* gene transfers becomes safe and efficient.

In summary, gene transfer represents a unique opportunity to treat a variety of cardiovascular diseases pertinent to the ageing population. Success will require new vectors as well as better model



systems in which to test these vectors. Furthermore, stringent testing of both viral and non-viral vectors in controlled trials with therapeutic genes will be necessary prior to their application in clinical practice. It must be remembered that gene therapy is a relatively young discipline. For its promise to be realised, patience is required.

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## Chapter 12

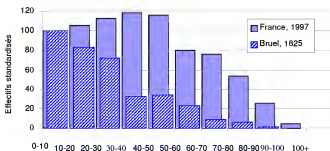
### THE IMPLICATIONS OF INCREASING THE HUMAN LIFE SPAN

by

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The increase in the number of elderly persons aged 60 or more has been the main demographic change in the OECD countries during the 20<sup>th</sup> century. Today, our societies benefit from healthy, active seniors aged 65 years to at least 75 years old. In the 21<sup>st</sup> century, a new segment of the population, the oldest old, nonagenarians and centenarians, will increase remarkably (Figure 1). The most spectacular aspect of this demographic trend will be the explosion in the number of centenarians, which has doubled each decade (Figure 2).

Figure 1. The population of Bruel-en-Vexin, 1625 (n=293) compared with the French population, 1997

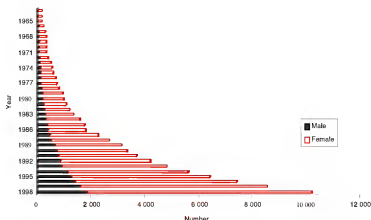


Source: Bois (1989); Besumel *et al.* (1999).

In the 1960s it was thought that the probability of death would reach 100% around the age of 110, considered as the limit of the human life span. Ten years later, in the 1970s, the same limit was postponed to the age of 115. Vaupel *et al.* (1998) show that the mortality trajectory no longer reaches 100% but reaches a plateau where the percentage dying each year is slightly under 60%. Rather than a limit to human longevity in terms of precise age, there is a new concept, the "plasticity of longevity". Rather than a maximum life span, the mortality rate for frail old persons appears to be around 60% per year.

Figure 2. Generational differences in the number of centenarians in Japan

Number of centenarians, 1963-98



Source: Tauchi et al. (1999).

In this context, healthy ageing and the expectancy of an active life are of the utmost importance. The World Health Organization (WHO) recently proposed to compute disability-adjusted life expectancy (DALE), a single measure allowing the comparison of the health status of different populations. However, for OECD countries, which are experiencing very low levels of mortality and a huge increase in the number of nonagenarians and centenarians, it is necessary to monitor the increase in life expectancy and to assess the average duration of life without disability (functional limitations or activity restrictions) or without loss of physical independence, *i.e.* disability-free life expectancy (DFLE) and active life expectancy (ALE). The OECD, WHO Regional Offices for Europe and for the Western Pacific, the European Union and the G7 recognise this.

Moreover, it is essential to distinguish between functional limitation and restriction of activity. Most of the oldest old experience physical or cognitive functional limitations. Not all are dependent in terms of the basic activities of daily living. There is no necessary link between functional limitation and restriction of activity. The challenge for biotechnology is to keep the oldest old robust and vigorous for as long as possible, *i.e.* to maintain activity among the frail elderly with functional limitations and prevent a further decline that results in physical dependency. Several strategies, ranging from biological (*e.g.* hormone replacement therapy) to social and environmental modifications, should be used to promote healthy ageing. Additional strategies need to be developed.

In conclusion, abilities can be restored and built on, potential can be developed, responsibilities can be changed and the environment adapted. There is much that the oldest old can do, might do, must do and wish to do, and this offers many avenues for developing new technologies for a healthy ageing society.

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## *Chapter 13*

### **BURDEN OF DISEASE AND DISABILITY-ADJUSTED LIFE YEARS A FOCUS ON HEALTH PROBLEMS AT OLDER AGE**

*by*

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#### **Introduction**

A first step in setting priorities to improve health at older ages is to take stock of the size and distribution of health problems in the elderly. Mortality and health-related loss of quality of life are the main issues. Any description of health status at the population level would need to take both these elements into account. To compare the size of different health problems, a summary measure is required. The disability-adjusted life year (DALY) is a measure of population health that integrates years of life lost owing to premature mortality and "healthy" time lost owing to illness, disability or injury, weighted for severity. For setting priorities, information from the Victorian Burden of Disease Study can be used to quantify (in DALYs) the burden of disease.

#### **Methods**

The DALY is a health-gap measure which combines at the population level severity-weighted healthy time lost to illness, disability or injury with loss of years of life owing to premature mortality and compared this to a normative goal of survivorship. In other words, the burden of disease in DALYs is the gap between the current health status of a population and an ideal in which everyone lives into old age free of disease. Life expectancy and disability-adjusted life expectancy (DALE) are alternative summary measures of population health. Figure 1 shows these measures in a survivorship diagram.

The Victorian and Australian Burden of Disease studies (Vos and Begg, 1999a; 1999b; Mathers *et al.*, 2000), which were conducted between 1998 and 1999, shared a common methodology, adopting a number of changes to the methods used in the Global Burden of Disease (GBD) study (Murray and Lopez, 1996) to adapt them to the Australian context. First, the main results were presented with uniform age weights. Second, the life expectancy of the 1996 Australian cohort was taken as the normative survivorship goal. The cohort life expectancy is calculated as the more usual period of life expectancy with the addition of a correction for future mortality rates based on observed mortality declines in the past. Life expectancy at birth for the 1996 Australian cohort was 81.5 years in males and 85.7 years in females. The Global Burden of Disease (GBD) study used a standard life table as the

comparator with a life expectancy at birth of 82.5 years in females and 80 years in males. Third, the severity weighting for non-fatal health states was largely drawn from a Dutch study (Stouthard *et al.*, 1997) and the GBD's disability weights were only used for health states for which there was no Dutch weight.

**Figure 1. Three types of summary measures of population health in a survivorship diagram**

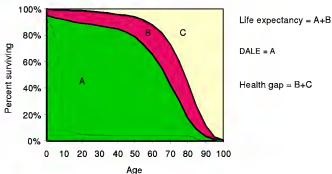


Figure 2 gives examples of disability weights for health states ranging from mild to severe. Eczema is at the mild end of the spectrum, and severe dementia has a very high rating. The disability weight of 0.94 for severe dementia means that one year lived in that health state represents a 94% loss of health. Fourth, an adjustment was introduced for co-morbidity between mental disorders, between physical conditions at older age, between congenital disorders and between injuries. While this is not a comprehensive adjustment for co-morbidity, it is an important new contribution to the method.

**Figure 2. Examples of disability for a range of mild to severe health states**



Source: Stouthard *et al.* (1997).

The Australian studies share a number of guiding principles with other burden of disease studies. First, analyses made the best use of the available data sources, which describe 176 diseases and over 400 associated health states. Second, all information was subjected to a rigorous check of internal consistency using the DISMOD software developed at Harvard University. The programme calculates



prevalence, average duration and mortality estimates that are consistent with input variables of incidence, remission and fatalities. Third, transparency was an important principle. Given that data sources were not perfect and that quite a few assumptions – sometimes, leaps of the imagination – were needed to make estimates, it was deemed essential to present the analyses for public scrutiny, and all the worksheets were put up on the Web. Another important issue was to uncouple epidemiology from advocacy, not a small issue. Dialogue continues with advocacy groups that say, “You have only estimated a few hundred people with our disease, but we think it is at least tens of thousands.” It is important to look closely at what the figures actually show and to indicate clearly the criteria for inclusion and exclusion.

## **Results**

### ***Disability-adjusted life expectancy***

Period life expectancy is the life expectancy measure that is most typically reported. It is an artificial measure that asks: If current mortality rates by age continue indefinitely into the future, what will the average life expectancy be at each age? Most often this is presented as life expectancy at birth. In Victoria, the 1998 period life expectancy was 76.8 years in males and 82.2 years in females.

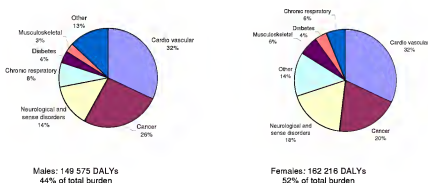
However, the reality is different. A child born today in Victoria can expect to live longer than the figures calculated by a period life expectancy because mortality trends are likely to continue to decline. Taking these future declines into account, the cohort life expectancy is six and a half years more than the period life expectancy at birth in males and five years more in females. Thus, if declining mortality trends continue, the difference between male and female life expectancies will grow smaller.

In 1998, disability-adjusted life expectancy in Victoria in 1998 was 69.5 years in males and 74.7 years in females, 8.9% below the unadjusted period life expectancy at birth in both men and women. In other words, on average, seven years of life expectancy were lost due to ill health. In comparison, life expectancy for 65-year-olds in 1998 was 16.7 years in men and 20.4 years in women, and over 20% of the remaining life expectancy was lost due to ill health. The loss of health in terms of life expectancy is proportionally greater at older ages. While the correction for disability reduces life expectancy at birth by about 8-9%, the correction rises steeply with age. At age 90, more than 30% of the remaining life expectancy is lost owing to ill health.

### ***Burden of disease***

The burden of disease in the population over 65 represents 44% of the total Victorian disease burden in males and 52% of the total burden in females (Figure 3). Cardiovascular disease and cancer are important contributors to the burden of disease in both males and females. The inclusion of non-fatal health outcomes highlights the importance of categories such as neurological and sense disorders, chronic respiratory disease and musculoskeletal disease. These would not have received much attention if only mortality-based measures were used. The estimates for neurological and sense disorders are driven by dementia, hearing loss, vision loss and, to a lesser extent, conditions such as Parkinson's disease. Osteoarthritis dominates the musculoskeletal disease estimates.

**Figure 3. The burden of disease in elderly Victorians by major disease category and sex, 1996**



Turning to individual diseases, ischaemic heart disease and stroke (classified under cardiovascular disease) are the main contributors to the burden of disease in elderly men and women, followed in males by emphysema (COPD) and lung cancer.<sup>7</sup> Tobacco-related conditions are typically of lesser importance in women. However, the tobacco-related burden is rising in women, while its significance is declining in men. Hearing loss is ranked seventh in the burden of disease in elderly men in Victoria. Osteoarthritis is ranked fourth in women, while dementia is an important contributor for both men (fifth) and women (third) (Figure 4).

**Figure 4. Top ten conditions contributing to the burden of disease in elderly men and women, Victoria, 1996**

Males	Females
1. Ischaemic heart disease	1. Ischaemic heart disease
2. Stroke	2. Stroke
3. Emphysema (COPD)	3. Dementia
4. Lung cancer	4. Osteoarthritis
5. Dementia	5. Emphysema (COPD)
6. Prostate cancer	6. Diabetes
7. Hearing loss	7. Breast cancer
8. Diabetes	8. Bowel cancer
9. Bowel cancer	9. Lung cancer
10. Osteoarthritis	10. Hearing loss

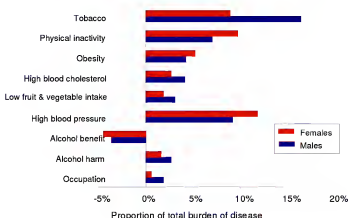
<sup>7</sup> Emphysema and chronic bronchitis together comprise chronic obstructive pulmonary disease (COPD).

Hearing loss is estimated to be the largest contributor to disability in males. There is some doubt about the accuracy of that result. It is influenced by a weakness in the methodology of deriving disability weights that does not do very well at distinguishing severity weights for relatively minor conditions. Because hearing loss is extremely prevalent – half of middle-aged men in Australia have at least mild hearing loss, and it increases with age – it is a very important contributor. Dementia, stroke and macula degeneration in women also appear as important contributors to the burden of disease (Figure 5).

**Figure 5. Top ten conditions contributing to the non-fatal burden of disease in elderly men and women, Victoria, 1996**

Males	Females
1. Hearing loss	1. Dementia
2. Dementia	2. Osteoarthritis
3. Stroke	3. Hearing loss
4. Osteoarthritis	4. Macula degeneration
5. Ischaemic heart disease	5. Ischaemic heart disease
6. Emphysema (COPD)	6. Stroke
7. Benign prostatic hypertrophy	7. Parkinson's
8. Prostate cancer	8. Emphysema (COPD)
9. Parkinson's	9. Breast cancer
10. Diabetes	10. Incontinence

**Figure 6. The burden of disease attributable to selected risk factors in elderly Victorians, 1996**



One can also present the burden of disease in terms of the contribution of selected risk factors (Figure 6). Because many of the diseases linked with these risk factors are more prevalent at older age and cause more disease burden at older age, the attributable fractions of disease burden are much

higher in the elderly than in the whole population. Tobacco is the largest risk factor, contributing 16.4% to the disease burden in males and 8.9% in females. Physical inactivity, obesity, high cholesterol, low fruit and vegetable intake and high blood pressure all contribute significantly to the burden of disease. In the case of alcohol as a risk factor, both the associated benefits and harm were calculated. In the elderly the benefits clearly outstrip the harm. That is because most Australians (claim at least) that they drink moderately.

In projections of the burden of disease in 2016, ischaemic heart disease remains high on the list although major declines are expected. Also expected are continuing declines in tobacco-related conditions in men, an increase in tobacco-related conditions in women, and a number of quickly rising conditions like dementia, prostate cancer, and also diabetes and melanoma in men (Figure 7). For this reason, the contribution of DALYs in the elderly, as a proportion of the overall burden of disease in Victoria, is expected to rise from 44% to 50% in men and from 52% to 56% in women in the year 2016.

**Figure 7. Ranking order of the burden of disease in the elderly by sex, Victoria, 1996 and projections for 2016**

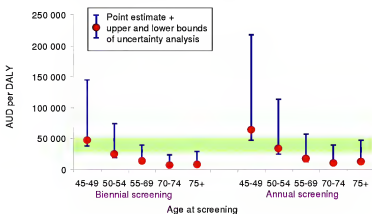
Males			Females		
Ischaemic heart disease	1	1	Ischaemic heart disease	1	2
Stroke	2	7	Stroke	2	6
Emphysema (COPD)	3	8	Dementia	3	1
Lung cancer	4	6	Osteoarthritis	4	4
Dementia	5	4	Emphysema (COPD)	5	3
Prostate cancer	6	3	Diabetes	6	7
Hearing loss	7	5	Breast cancer	7	8
Diabetes	8	2	Bowel cancer	8	11
Bowel cancer	9	10	Lung cancer	9	5
Osteoarthritis	10	11	Hearing loss	10	9
Melanoma	19	9	Macula degeneration	11	10

## Discussion

The size of Victoria's health problems gives an indication of potential areas for health gain. However, for setting priorities for health services, additional information is needed on the cost effectiveness of intervention options. The following example of a cost-effectiveness analysis of screening for bowel cancer by faecal occult blood testing (Carter *et al.*, 2000) illustrates this point.

Figure 8 compares the cost-effectiveness ratios of annual versus biennial screening for bowel cancer screening by age group screened. The horizontal indicates an arbitrary cut-off of AUD 30 000 to AUD 50 000 per life year saved. Below this amount, interventions are frequently classified as cost-effective in Australia. The results of the study indicate that biennial screening for bowel cancer in Australia is cost-effective at ages 55 and above, possibly also in the 50-54 age group, but certainly not at younger ages. Annual screening is less cost-effective but the absolute benefits are greater than for biennial screening. This information has a direct link to policy decision making, as the Australian government is contemplating the introduction of such a screening programme.

**Figure 8. Cost-effectiveness ratios for screening for bowel cancer by faecal occult blood testing by age group and annual or biennial screening methods**



Such studies not only help to set priorities for provision of health services, they can also be used to set priorities for health research. The Global Forum for Health Research has developed a five-step procedure to set priorities in health research. The main aim of the Global Forum was to address the issue of the 90/10 gap, where 90% of health research funds are spent on the health problems of only 10% of the world's disease burden. The first step is to determine the size of the health problem. Next, what are the reasons for the persistence of this burden? Why has it not disappeared like other causes of disease burden? The third step examines the adequacy of the current knowledge base. Is current knowledge about the disease adequate, or is new information needed to reduce the burden of disease? The fourth step asks what a concerted research and development effort may achieve. This might involve basic research into the causes of disease in order to develop new technologies for intervention, for example new biotechnological solutions to health problems in the elderly. However, in many cases, when trying to reduce the size of the burden it is far more important to make better use of available interventions and to explore ways of increasing their use among people who might benefit. Last in this five-step procedure is the question of whether the current level of R&D is adequate when compared to the promise held out by investments in more R&D.

## Conclusion

Evidence on the size of a health problem and the cost effectiveness of various interventions can contribute to decision-making on health priorities. DALYs and health burden calculations can be a useful methodology for measuring population health problems as well as for quantifying health benefits. A common methodology for economic analyses enhances the ability to make comparisons across very different health problems and health interventions.

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## *Chapter 14*

### **INTERNATIONAL EPIDEMIOLOGICAL PERSPECTIVES ON CANCER**

*by*

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Cancer has historically been thought of as a well-defined disease, whose epidemiology is easier to describe than that of other diseases. Today, however, new diagnostic techniques have revealed the disease's heterogeneity.

International figures on the incidence of cancer show that in persons over 65 years of age, it is much higher in North America than in other developed countries. In Europe, it is slightly higher in central than in northern regions. The incidence is approximately the same in southern and eastern Europe and Japan is in line with average European figures. The incidence of cancer is twice as high in males as in females. While incidence rates are revealing, other parameters of cancer epidemiology – survival and prevalence – are less well known and much less studied.

During the past ten years, EUROCARE – the European Cancer Registry Base – has examined the survival and care of cancer patients. At present, EUROCARE involves 60 population-based cancer registries in 20 European countries. The data presented in this chapter, however, concern 17 countries. While the databases share some common ground, there are also some differences. For example, only some countries index survival (adjusted for sex and case mix), and some countries, such as the Nordic and Eastern European countries, have national data whereas others (*e.g.* France and Italy) cover only 10% of the population. Hence, it is important to note that the results discussed in this chapter are not comparisons among countries but among different populations.

#### **Survival**

Interpreting measures of survival is complex. As survival is the interval between the date of diagnosis and the date of death, survival may increase either because death is postponed or because there is earlier diagnosis. It is very difficult statistically to disentangle these two factors. However, the major aim of EUROCARE has been to interpret survival differences.

Perhaps the most striking finding resulting from the analysis of EUROCARE data is that cancer survival rates in the United Kingdom and Denmark are almost 20% lower than in Sweden and France where cancer survival is longest. This has been much discussed in the last few years and has led to important political decisions in the United Kingdom which have resulted in increased financial support for oncology.

The survival rate for all cancers, except non-melanoma skin cancer, is highly dependent on age. Relative survival, *i.e.* corrected for mortality from other causes, is the ratio between the observed survival and the expected survival of the general population with the same age. Survival is better in younger than in older subjects at both the one-year and the five-year mark following diagnosis. This is true for every cancer site. The relative risk of death for cancer patients aged 65-99 is higher than for patients aged 55-64 for both men and women. The difference in the relative risk of death between the two age groups is greater at the one-year than at the five-year mark. This suggests that most of the difference is due to later diagnosis in older subjects.

Survival rates are higher for women than for men at all age groups. This is due not only to the different mix of cancers in the two sexes but also to the higher survival rate for women with a particular type of cancer. In a first tentative comparison between Europe and the United States, the average length of survival among EURO CARE populations was 38% (with the highest survival rate at 42%). In the United States, the rate is slightly above 50% for all cancers. Except for stomach cancer, survival is longer in the United States than in Europe. However, as mentioned above, it is difficult to know the reason for this difference. Furthermore, there may also be issues of data quality and consistency, such as differences in the quality of registration, completeness of follow-up, or the definition of illness.

Examining comparative survival figures for some specific cancer sites shows that survival from colon cancer is longer in the United States than in Europe, especially among the elderly. For breast cancer, the effect of age on survival is less striking although there is a big difference between Europe and the United States for older women. The notable improvement in survival trends in Europe concerns older women and suggests that Europe is approaching a pattern similar to the United States. Survival from stomach and breast cancer is longer in Japan than in Europe but it is not known whether this is due to differences in diagnostic reporting by pathologists in Japan, the United States and Europe.

## **Prevalence**

Prevalence – the number of cases in a population at a point in time – is a function of incidence and survival. The EURO PREVAL project, which followed on from the EURO CARE project, provides prevalence figures and its first results indicate that the overall prevalence of cancer in Europe is about 8%. This figure is an average derived from 35 cancer registries in Europe. The average prevalence in the United States is approximately double, and this is due to the higher rates of both incidence and survival.

In general, incidence is a major determinant of prevalence. Where incidence is higher (*e.g.* in central Europe), prevalence is higher; where incidence is lower (*e.g.* in eastern Europe), prevalence is also lower.

Attempts are also under way to compare survival and prevalence in Europe and the United States. For breast cancer, prevalence is about 50% higher in the United States than in Italy – except in the state of Utah, which has a much lower incidence of breast cancer. For colon cancer, prevalence in the United States is double that in Europe. For stomach cancer, prevalence is over ten times higher in Italy than in some American registries. The extent of comparative analysis is restricted by data limitations.

How many of the patients with cancer today are actually cured? For certain types of cancer, this can be estimated statistically. That is, when relative survival is the same as survival of the general population, it is possible to say that patients are cured. For colon cancer, for instance, patient survival



five to six years after diagnosis is the same as that of the general population. Those who are not cured, who have or will have recurrence, fall into a category called premorbid prevalence.

The first estimate in the cancer registry for northern Italy concerns colon cancer with overall survival corrected for general mortality. Recurrences occur in 60% of patients with colon cancer. For all types of cancer, at the end of the 1980s, the proportion of patients in Italy cured of cancer is estimated at about one-third of patients, more of whom are female than male. This share for Italy is very similar to the average in other European countries.

Average survival for subsequently fatal cases, interestingly, is increasing for men but decreasing for women. This is because a fraction of women who were expected to die yesterday are saved today, resulting in an increase in the proportion of women cured. This is due to improved results for breast cancer. For men, the opposite trend is seen, largely due to lung cancer. The proportion of cured patients decreases steeply with age. One-quarter of female patients over age 75 are cured but only 14% of male patients. If deaths due to cancer were eliminated, life expectancy in Italy would increase by about four years for men and by slightly more than two years for women.

Prevalence is a major factor in the costs of cancer care. These are very high just after diagnosis, when primary treatment is given, and then tend to decrease. This stage is followed by a period of clinical surveillance where costs are usually relatively low, but if recurrences occur costs increase again. With the epidemiological profile described above it may become possible to describe the cost of care. Perhaps more importantly, it may be possible to examine the cost of cancer care when prevalence changes.

#### **IV. HEALTHY AGEING: SOCIAL POLICIES AND TRADE-OFFS**

The chapters in this section first note the many policy challenges associated with an ageing population. These can be summarised as the need to provide services to improve active ageing and quality of life while at the same time respecting budgetary constraints. The chapters then spell out policies options that can help address these challenges.

A consistent message is that the elderly represent a heterogeneous population, with varying needs, degrees of need, skills and capacities. In many ways, the elderly are more diverse than younger adults. Health and social services need to reflect this diversity and be responsive to the needs of individual citizens. A further key message is that the ageing phenomenon reflects a change in the individual's interaction with the environment. For example, the impact of a functional loss largely depends on the social support network, transport and home environment. The chapters consistently argue for an integrated approach to policy development which takes into account a wide range of services and perspectives. The common thread is the need to find effective means either to adapt the environment to the needs of the individual or to enable the individual to adapt to the environment. In either case, technology can play a crucial role.

## *Chapter 15*

### **LONG-TERM CARE FOR OLDER PEOPLE: RECONCILING BUDGETARY CONSTRAINTS AND QUALITY IMPROVEMENT**

*by*

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#### **Introduction**

The central challenge facing health and social care systems with regard to population ageing is to ensure good-quality, cost-effective services. This European view is based on observations in the member states of the European Union and refers to the scope for concerted EU action. It addresses four main areas: *i*) the relationship between demographic change and the need for health and social care; *ii*) the strategies used by European health and social systems to limit expenditure on health and social care; *iii*) the imperative of improving quality; and *iv*) reconciling budgetary constraints and quality improvement.

#### **Demographic change and the need for health and long-term care**

As a result of declining fertility and increasing longevity, the EU is ageing, although the rate differs among countries and especially among regions. In a large number of European regions, the population had stopped growing by the end of the 20<sup>th</sup> century and this be true in most EU regions before 2015. In some regions, populations may even decline before that date. The generation below 25 years of age constituted 31.1% of the population in 1995, and their share will drop to 27% by 2015, a decrease of some 11 million persons. The generation over 65 years of age will increase, significantly but unevenly, throughout the EU. In some parts of France, Italy and Spain, the 80-plus generation will represent 7-9% of the population, compared with an average 3.9% in 1995. The average age of the population will increase from 38.3 years in 1995 to 41.8 in 2015. In some regions in eastern Germany, northern Italy, central France and northern Spain, the average age will be between 44 and 50 years.

Growth will be fastest among those over 80 years of age. A large share of the total increase in this group over the next 25 years, estimated at 62%, will take place in the period 2000-05, which will see a 25% or greater increase in Belgium and France and nearly as much in Italy and Austria. In 2025, 7.1% of Italians, one in every 14, will be over 80. Growth will also be fast in Germany, owing to the pre-war baby boom, followed by Denmark, Sweden and Ireland.

The eastern European countries are also experiencing demographic ageing. In all except Poland, there will be a decline in the total and working-age population before 2010. The EU shares the

phenomenon of demographic ageing with other regions. Over the next 20 years, the trend will be most pronounced in Japan. At this point in a discussion of demographic trends, data on dependency ratios are usually cited. This will not be done here because such data are at best misleading, crude and simplistic; at worst, they may be harmful to the cause of rational policy debate. The policy implications of demographic change are not simply a matter of absolute numbers in different age groups.

First of all, it must be remembered that increasing longevity is an indicator of social and economic progress: the triumph of science and public policy over many of the causes of premature death that cut lives short in earlier times. Therefore, the emergence of more balanced age structures should be recognised as one of the great achievements of the 20<sup>th</sup> century. Nevertheless, these demographic changes present challenges to policy and practice in all sectors of society.

Second, there is no simple linear relationship between demographic change and demand for spending on social protection, still less with the levels of such spending. For example, with regard to health and social care, the level of need for paid care depends on range of social factors, not health status alone. In all EU countries, albeit to different degrees, the family provides the initial response to the need for help and support. The primary sources of care are unpaid family and friends, including the care provided by older people themselves to their spouses and others. Thus, marriage patterns, fertility, household composition and living arrangements are all important. Therefore, the demand for formal care, public and private, is a function of both health status and family relationships.

It is predicted that the number of people's disability-free years will increase in the next century (Tallis, 1992) but the evidence so far is inconclusive (Bebbington, 1991; Dunnell, 1995; Department of Health, 1992). Other population trends provide a more certain picture. Older people living alone tend to make greater use of formal services than those living with others. It should be noted that advanced old age and living alone are correlated, and in the EU an increasing proportion of this population lives alone. Given the primacy of family care, it is likely that the increase in family breakdown and divorce both among older people and their children will affect the demand for formal care. However, the evidence to date is inconclusive. Similarly, the increased participation of women, the primary caregivers, in the labour force has increasingly strained their capacity to fulfil this role.

Although more older people in the EU today have children than in previous generations, family size has declined dramatically over the course of this century. As a result, the pool of potential family caregivers has decreased. Over the next decade or so, however, the numbers of those aged 45-64, the main age group from which family caregivers are drawn, will rise in some countries.

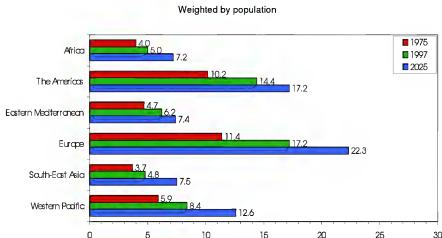
The need for paid care is therefore, to a large extent, an outcome of the interaction between health status and family relationships. In certain instances, there is a more direct connection between health in old age and the demand for formal services, including acute episodes such as stroke and long-term impairment such as dementia. Cognitive impairment is one of the main reasons why older people require long-term institutional care. The prevalence of moderate or severe cognitive impairment rises steeply with age, from 2.3% in those aged 65-74, to 7.2% in those aged 75-84, and to 21.9% in those aged 85 and more. Dementia causes acute problems for family caregivers and there is a need throughout Europe for special measures to support the care of this group.

The idea of a triangular relationship between the family, the state and the private sector helps to remind us that health and social care depend on different inputs and that the government need not provide care directly but may subsidise or regulate care in other sectors. In practice, what matters is the interaction between the different sectors. Within the formal or paid sector, the role of health

services for the older population is increasingly being confined to acute episodes and rehabilitation, whereas social services have responsibility for long-term care.

Declining fertility is a global phenomenon and is closely connected with economic development. The EU birth rate fell below the replacement rate 20 years ago and for Europe as a whole it is equal to the replacement rate. One indicator of the implications for social care of the changes in fertility in combination with the universal increase in longevity is the parent-support ratio (PSR), the population over age 80 divided by the population aged 50-64. Because Europe aged earlier than other regions, its PSR is the highest in the world and is likely to remain so for the next 25 years (Figure 1).

**Figure 1. Parent support ratios in WHO regions**



Source: WHO, 1998, p. 39.

The trend in crude age-dependency ratios suggests increasing tax burdens on the working population. However, this scenario rests on the classic economic assumption that present trends will continue far into the future. In fact, the main issue for pension funding is not population ageing *per se* but its combination with changes in birth rates, the structure of employment and the practice of retirement. In a very short space of time, there has been a major restructuring in most EU countries owing to the truncation of employment prior to pension ages (Kohli *et al.*, 1991). In some EU countries the trend has been openly encouraged by public policy. Thus, paradoxically, as longevity has increased, the age at which people cease economic activity has fallen. Since the 1950s there has been an average increase in longevity in the EU of around ten years and a parallel decline in the age of retirement. Esping-Andersen (1996) stated that Europe has “doubled pension benefit years and cut contribution years by around 25%”. The realisation that early retirement has created problems in terms of employment and social protection has led most EU governments to abandon or curtail this trend.

Arguably, it is not demography that is the main issue for social policy and social protection but the growing insecurity of labour markets, on which most pension systems depend, combined with the rise in divorce and the decline in fertility. If there is a crisis in some EU welfare states it is the growing incompatibility between the assumptions underlying social protection, including the stability of the work force, and changing socio-economic structure.

Finally, the biological fact of ageing is only part of the story and actually reveals little about the social impact or the policy implications of ageing. Here, sociology is more helpful than biology. Age is a social construct, and social policy plays a crucial role by defining the age at which people enter pension systems and therefore become "old". Because the meaning of age is determined by social processes, the impact of ageing is influenced by social policy. If, for example, one looks back over the last 30 years at the reasons for the growth of pensions expenditure in all OECD countries, it is clear that demography played a minor role compared to policy decisions (OECD, 1988). In other words, there is nothing inevitable about the impact of ageing on society. The policy process determines whether or not countries age successfully.

### **The challenge of cost containment**

It is essential to emphasise the uniqueness of the institutional structure within which ageing is taking place in the EU. Most of the world's developed welfare states, and all of the countries that devote the highest shares of their national income to social expenditure, are in the EU. For example, in 1997 the EU as a whole spent around 12% of GDP on pensions, compared with 4% in the Western Pacific (European Commission, 1998). Within that average, however, there are significant variations among EU countries, particularly on a north-south axis. Thus, while the EU contains fully developed welfare states (mainly in the north), there are also countries (mainly in the south) whose welfare systems are still at an early stage of development. For example, Austria and Finland spend twice as much of their national incomes on pensions as Greece and Ireland. Nonetheless, even the most underdeveloped welfare systems of southern Europe are at least twice as effective in relieving poverty as that of the United States (European Commission, 1995). In other words, the EU is in a much better position than other world regions to respond to the challenges of population ageing.

Despite that apparently advantageous position, the ageing of the population has coincided with the end of the exponential growth period of European welfare states. The reasons for this are complex. As Esping-Andersen (1996) has noted, the crisis in welfare states has occurred despite continuing prosperity. Attention has focused mainly on the growth of spending on pensions, but general concerns about the financial problems of welfare states has also led to questions about the cost of health and social services. Although there is considerable variation among EU countries in the priority given to these questions and in the extent to which their welfare systems have been perceived to be in crisis, there is no doubt about the general political priority that has been given to cost containment. Indeed, cost effectiveness is an imperative in all European health and social care systems. So far, three basic strategies have been employed to contain the public expenditure costs of health and social care.

### ***Improve efficiency***

Improving efficiency is the heart of the cost-effectiveness imperative – the effort to reduce costs while maintaining the volume and quality of output. Here it is important to bear in mind the distinction between technical and distributional efficiency. For example, the production of services by a local services system may be technically efficient but would not be if an alternative allocation would achieve a greater impact. This difference is clearly illustrated in the case of institutional care vs. community care: the former may be technically efficient but the latter is likely to affect a much larger proportion of the population.

Strategies to improve technical efficiency have focused on the management and financing of services. For example, "quasi-markets" have been created in health and social care. These entail a separation of the functions of "purchasing" and "providing" within the public sector and the use of

private sector management techniques such as privatisation of public services. Evidence concerning the impact of such changes is decidedly mixed, though it must be said that good-quality before-and-after data are hard to come by. The United Kingdom led the way in the privatisation of long-term care services for older people in the 1980s. This led to a huge expansion in residential care and, consequently, a huge rise in public expenditure. What is quite clear is that even in the most extreme cases of privatisation and marketisation, very strong public regulation of the market has been necessary.

Strategies to improve distributional or allocative efficiency include the shift from hospitals to community services that is taking place everywhere in western Europe. The assumptions behind this policy are that hospital care is too medicalised, expensive and dependency-creating, whereas community care maximises existing family-based resources and is therefore more efficient. The trend away from institutional towards community care is a general one, but there is little evidence about its impact. What there is demonstrates that this policy accords with the preferences of both older people and family caregivers. Another measure designed to increase distributional efficiency is the retargeting of home-care services. For example, in Finland, Sweden and the United Kingdom, there is a tendency to increase the amount of help going to those in greatest need while reducing it to those with "less" need on the assumption that they can take care of themselves or purchase private care. The danger here, of course, is that services' capacity in terms of prevention is also reduced.

### ***Increase revenue***

There are two main strategies for increasing revenue: user charges or co-payments and cost-shunting. While universal access to health care (if not to pharmaceutical or dental care) is generally accepted in Europe, this is not the case for social services. The practice of charging users is widespread. Means testing is commonly used to determine user charges. In some countries, these charges create a barrier to effective collaboration between health and social services. Moreover, the shift from hospital care to community care results in an increase in the contribution of user charges to total costs. In the United Kingdom, the health service has increased the discharging of older patients so that local authority social services departments become responsible for them. In other countries, disputes between social insurance and local authorities are common. Alternatively, funds may be sought from the housing sector by redefining residential care. Such interdepartmental conflicts are characteristic of systems under financial pressure and signal the absence of a comprehensive approach to the health and social care needs of older people.

### ***Rationing***

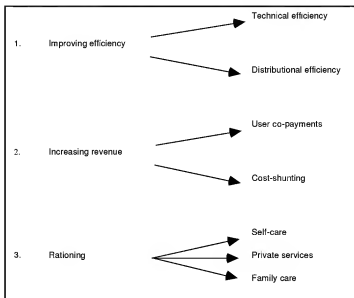
The third approach to cost containment is rationing services or failing to increase expenditure in line with need and, as a consequence, reductions in the scope of services. Various assumptions underpin this strategy. It has been argued that pensioners are more affluent than previously and are able to purchase services privately. Frequently, it is assumed that in the absence of paid care there will be an increase in care from family members or the wider community. At the very time when the family is less able to increase care of older people and the elderly are increasingly reluctant to be dependent on their children, there is renewed emphasis on the responsibilities of families to take care of their frail members. Some countries, such as Germany, have introduced care insurance or home-care allowances to provide economic incentives for unpaid care.

Needs testing has also been used to restrict the numbers of older people eligible for public home care in Finland, Sweden and the United Kingdom. The danger with restrictive needs testing, apart

from neglecting prevention, is that decisions concerning allocation will become “medicalised” and exclude users of services and their caregivers. Age discrimination can also restrict access to health and social care and therefore operate as a rationing device.

These three strategies for cost containment may be represented diagrammatically (Figure 2). It is important to recognise that the pursuit of a particular strategy may result in increased expenditure elsewhere or in other undesirable consequences such as additional social exclusion. Ideally, before any strategy is chosen, a study would be undertaken of its likely impact not simply in terms of net expenditure, important though this is, but also in terms of the overall goals of the services.

Figure 2. Cost containment strategies



### A quality imperative?

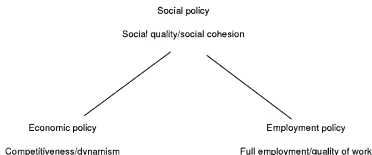
Although cost efficiency has been the dominant imperative in EU health and social services for the past decade, the member states have also engaged in consistent efforts to improve the quality of these services. Thus, despite or perhaps because of budgetary constraints, there has been a wide range of innovations in the care of older people, particularly in community-based support. Of course the impact of innovation should not be overstated: the main source of care for older people remains the family, and when paid care is received it is likely to be in the form of traditional home help. Nonetheless, the evidence of considerable innovative zeal in this field does suggest that quality improvement has moved up the policy agenda. Moreover, there are good reasons to believe that it may itself become an imperative for health and social services. Five main points support this contention.

First, in the European model of development, there is the implicit commitment to quality of life, which has recently become more explicit. For many years, leading European policy makers, like Allan



Larsson, have pointed out that the European model has two dimensions: economic growth and competitiveness on the one hand and solidarity and high-level social protection on the other. In its latest document on social policy, the European Commission portrays a dynamic interaction between three sets of policies: social, economic and employment (Figure 3). The concept of “social quality” was developed under the Netherlands presidency as an expression of the social dimension of Europe. Social quality is the extent to which citizens are able to participate in the social and economic life of their communities under conditions that enhance their well-being and individual potential. It may be measured by reference to the levels of socio-economic security, social cohesion, social inclusion and individual autonomy enjoyed by citizens.

**Figure 3. The Diamantopoulou policy triangle**



Source: European Commission, 2000, p. 6.

Following this approach, the new European Social Policy Agenda commits the EU to the promotion of quality: the quality of work, the quality of social policy and quality in industrial relations (European Commission, 2000). The EC has had a long-term commitment to combating social exclusion, but Article 137 of the Amsterdam Treaty puts the fight against social exclusion at the very heart of the European social quality mission; this is therefore becoming an increasing priority for member states. For older people, special measures could be developed to overcome exclusion among some of Europe's most deprived citizens, especially very elderly and frail women and those suffering from dementia.

Second, although Europe has some of the most highly developed health and social services systems in the world, there are still major variations in their quality and quantity and, in some cases, between different social groups and spatial locations. For example, there are significant variations in expenditures on health care and in per capita spending on the older age groups. It is true that spending is a poor proxy for quality, but the fact that, in some countries, the ratio of health expenditure on those over 65 to those aged 0-64 are more than twice the ratio in other countries, must in part at least signal a difference in quality. With regard to long-term care, the limited available evidence reveals substantial variations in the quantity of both home care and residential care, particularly between the north and south of the EU. In fact, in most member states, there is a gap between the need for care among older people and the supply of care from either family or paid caregivers. The failure to provide sufficient home-care services obviously means that some frail and vulnerable people and their family caregivers are placed under great strain, which, in turn, threatens the viability of their caring relationships.

Within member states there are often substantial inequalities in the provision of health and social care. Sometimes these are the result of local democracy, but sometimes they reflect the persistence of the "inverse care law", *i.e.* the supply of good-quality health services varies inversely with the need for them. There are indications in several member states, including the Netherlands and the United Kingdom, of concerted efforts to reduce some inequalities by refocusing health services on public health and primary care.

Third, there is a realisation that excessive concentration on technical efficiency may have resulted in distributional inefficiencies and a decline in the quality of care for some older people. In the United Kingdom in the 1980s, there was a perverse incentive, in the form of social security payments, for older people to enter residential care. The result has been an oversupply of such care, which coexists with shortages of home care, although the expressed preference of older people and their family caregivers is to remain in their own homes.

Fourth, there is the new consumerism among health and social service users, including older people and their family caregivers. These groups complain more openly about services' lack of responsiveness to their needs. The spread of pensioners' movements throughout Europe will give impetus to these criticisms and increase the pressure for change within health and social services. Similarly, family caregivers are becoming organised and arguing that health and social care systems take them for granted. Thus, both service users and caregivers are calling for greater participation in health and social services decisions concerning their care. They want services to respect their rights to self-determination and dignity. In other words, they consider the way in which a service is delivered to be an essential element of any assessment of its quality.

Finally, there is the professional commitment to quality. Health- and social-care services personnel are not passive bystanders in the quest for quality. Indeed, many have been at the forefront of quality improvements and the search for new ways of measuring both the quality and impact of their services. They have also been major initiators of research into quality of life. At present, several national research programmes focus on the quality of life of older people and how it may be extended, such as the Growing Older Programme in the United Kingdom, the Finnish Academy's Research Programme on Ageing and, at EU level, the Fifth Framework Programme which not only has quality of life as its main objective but has a key action on ageing and disability. This professional commitment is evident in the WHO policy of continuous improvement of the quality of health care in Europe. In addition to new approaches to measuring health status and quality, there is a wide range of methods to evaluate service quality; both signal a refocusing of health and social services towards the experience of patients and users. Together, these five factors put pressure on policy makers to improve quality of care for the elderly.

### **Active ageing: reconciling budgetary constraints and quality improvement**

Health and social service systems are faced with the twin goals of cost containment and quality improvement, though the former currently dominates. It appears possible to reconcile these apparently conflicting objectives.

There are two points of departure. On the one hand, ageing societies should expect to devote increasing proportions of national resources to their older populations; on the other hand, generations age differently and the health status of the present older population is not necessarily a good guide to that of future ones. In particular, social policy has a crucial role to play in determining the future demand for health and social care by older people. Europe has already seen improvements in the health of its older citizens and the compression of morbidity thesis is obtaining some support. Older

people are still, however, over-represented in hospitals and doctors' waiting rooms and in the use of medication. What is required now, therefore, is a strong policy emphasis on extending quality of life.

The cost containment measures reviewed earlier, which have been adopted in a piecemeal way by EU governments, have two deficiencies: they are reactive and supply-oriented. To balance the reactive responses to population ageing, a more active perspective is required. In other words, to extend quality of life among future cohorts of older people, efforts must focus on the whole of the life course and aim to prevent morbidity. As the WHO has put it, years have been added to life, it is also necessary to add life to years. This would affect the demand for health and social services and make quality improvement sustainable.

Such a strategy would entail, first, a refocusing of health services from sickness to promotion of health at all ages, from curative to preventive medicine. In most countries this would require closer collaboration between health and social services. Second, policies – economic and social, national and local – should be subject to quality impact statements to test how far they add to the quality of life of different groups. Third, with regard to extending quality of life in old age, a concerted effort to encourage active and healthy ageing is needed. An important aspect of this is the extension of economic activity by overcoming blockages such as age barriers in the labour market; this would also contribute to the revenue side of this equation. The European Commission has a very important role to play in disseminating examples of good practice in the employment of older workers and, under Article 129 of the Amsterdam Treaty, in initiating Community actions to improve public health and prevent disease. Additionally, Article 13 of the Treaty specifically mentions age discrimination and empowers the Commission to propose measures. For those outside the labour market, productive ageing should mean active citizenship, including engagement in voluntary activity.

In emphasising active ageing, there is an obvious danger that those experiencing dependency will be further excluded. This is not a real dilemma, however, because action should also be taken to include and add quality to the lives of the most frail and vulnerable. The focus of attention in this respect should be the maintenance of older people in their own homes. As noted above, the targeting of social care resources on those in greatest need has meant that the preventive role of social services has been neglected. There is an urgent need to provide low-level support, in partnership with families, designed to prevent the breakdown of caring relationships. This support should be seamless and not inhibited by bureaucratic and professional boundaries. Europe urgently needs more and better home care and other support for family caregivers.

As the report from the European Technology Assessment Network (ETAN) demonstrated, there is great potential for new technology to assist with both the inclusion of frail older people and the enhancement of their quality of care, with sufficient safeguards, of course. Moreover, new technology in the fields of telecare and telemedicine will make an important contribution to future growth and employment in the EU.

The ETAN report identified three broad areas of opportunities for innovation:

- ◆ Opportunities related to the extension of working life among older people, *e.g.* new modes of work, new organisational forms, new workplace technologies and new lifelong learning systems.
- ◆ Opportunities related to enhanced activity, mobility and quality of life, *e.g.* age-friendly design of transport equipment, housing and communication systems.
- ◆ Opportunities related to health, well-being and support, *e.g.* biological, social and medical research, telecommunications-based technologies for the delivery of seamless care.

The report listed eight priorities for research, technology development and innovation (RTD&I): lifelong learning techniques, technologies and methods for new modes of flexible work organisation, design for age-neutral product and process technologies, transport and mobility infrastructures, age-relevant information and communications technology applications for work, the domestic environment and support, understanding and prevention, technologies for seamless care and support, and medical communications for decentralised health care (ETAN, 1998).

With regard to RTD&I opportunities, it must be remembered that innovation in any field requires recognition that technology is both technical and social in nature. This means that RTD&I programmes should be designed and operated according to some basic principles: user involvement in research and technology development, integration of social research and trans-generational design principles and interdisciplinary programme structures (ETAN, 1998, p. 26).

A policy for quality of life must also include those in residential and nursing homes. This means both enhancing the quality of institutional environments and enabling frail older people to take part in decision making. Finally, action is required to eliminate age discrimination in health services which excludes older people from certain procedures on grounds of age rather than need. A positive policy of non-discrimination would entail empowering older people to make their own choices and ensuring that they take personal responsibility for themselves. This focus on the inactive as well as the active fits in well with the Council of Europe's call for measures to counteract dependence, to empower dependent older people and to provide training for those working with them. It also reflects the emergence of a European policy on active ageing which, in line with the theme of the UN Year of Older Persons, is based on the vision of a citizen's Europe for all ages, in which all are valued and everyone has the opportunity to participate and contribute regardless of their age or other personal characteristics (Walker, 1999).

A cost-effective strategy to extend quality of life, therefore, would require health and social services systems to develop quality care that reflects some common principles: prevention, the promotion of active ageing, social inclusion, seamlessness, working in partnership with families and older people to share care more effectively and cost effectiveness. The combination of quality and cost containment necessitates a definition of quality that incorporates value for money. Health and social care should be appropriate, or "fit for purpose", effective in terms of outcomes and, as mentioned, cost-effective. The judgement about which source of care offers best value for money should not be determined only by cost efficiency but by effectiveness, accessibility and quality as well. This may imply a significant provider role for non-governmental organisations (NGOs) and the private sector – depending on the country – which means that governments have to fulfil the crucial role of regulation with regard to quality of services (and older people themselves must be central in the assessment and measurement of quality). In most countries, the achievement of this principled approach is inhibited by the artificial separation between health and social services.

## Conclusion

The 1997 Amsterdam Treaty gives a very important place to EU-level actions with respect to public health and combating social exclusion. The fight against social exclusion must be at the heart of any strategy to promote quality of life among older people. A combined public health and social inclusion strategy would make good sense. Indeed, there seems to be an opportunity to reorient health and social services towards extending quality of life in old age. Such a policy is good for everyone: older people, their families, society as a whole in financial terms, and younger generations as well, as it gives them something positive to look forward to.

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## *Chapter 16*

### **MEETING THE CHALLENGE OF ENSURING ACTIVE AGEING AND IMPROVED QUALITY OF LIFE**

*by*

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#### **Introduction**

Few things in economic and social life are predictable, but one that is predictable is the ageing of the population in most OECD countries. These countries will also experience a fall in the number of young people and in the number of working adults. The changing age balance in many societies will reshape their demographic, social and cultural structure over the next 25 years (Walker and Maltby, 1997).

The increase in the numbers of older people is not a surprise, because longer life has been an explicit objective, which is reflected in pension systems and improved health-care systems and social services. It is now more than ever necessary to prepare for the future challenges and opportunities that new technologies pose. What benefit can technology, especially biotechnology, provide for an ageing person? What will be the future role of pharmaceuticals in preventing and treating ageing? How can the middle-aged invest in their own future? How can technology assist those who take care of old people? How can older people gain greater control over daily life and greater autonomy? How can the negative consequences of technology be avoided so that social actions will always be accompanied by a striving for human dignity, autonomy and people's full involvement (Foresight, 2000)?

#### **What is ageing? What is active ageing?**

Ageing is a natural process, a cultural, social and physiological phenomenon that is becoming more fully understood owing to active, multidisciplinary research in the field. While most older persons in all societies live active, healthy lives and do not need any help, ageing may cause disabilities. A disability or loss of function is a change in an individual's relationship with the environment. Everyone needs help in coping with an increasingly complex environment. People wear spectacles and use telephones without being branded as disabled or in need of technical assistance.

Ageing people undergo sensory and cognitive changes. Their hearing and their sight are gradually impaired. They may also have difficulties in remembering recent events. The perceived health of an ageing person is, however, of the greatest importance. Persons of a given age are not a homogeneous group and it would be a grave mistake to speak of them as if they were. In fact, the elderly are more diverse than younger adults.

Two important OECD concepts should be mentioned here: *active ageing* and *ageing in place*. The OECD's *Maintaining Prosperity in an Ageing Society* (1998a) states that "active ageing reforms are those that remove undesirable constraints on life course flexibility and that strengthen support to citizens in making life-time choices". Policies for active ageing have to cover wide areas of life and maintain coherence of actions. The concept of active ageing brings with it a different way of looking at policies, a paradigm shift that can result in new insights. Such policies take account of the continuity of life and they are also targeted to younger people who will need support in later life.

Active ageing should be promoted and older people should be motivated to use all their resources to respond better to the challenges of ageing. Ageing in place is a concept that emphasises the need to give older persons the opportunity to remain in their own homes rather than be cared for in an institutional setting. Policies for ageing in place differ considerably from traditional policy approaches.

### **Key challenges for innovation**

These population changes should be viewed as positive opportunities for societies and economies (World Bank, 1994). The opportunity lies in innovative social, organisational and technological responses to the challenge of finding innovative solutions in global and national research and development, in technology, in cultural and in social welfare, as well as health policies. In many areas, social, organisational and technological innovation may significantly modify the effects of population change by promoting active ageing. The major challenges in promoting such policies are:

- ◆ Extension of working life.
- ◆ Improvement of accessibility in the environment and the activity, mobility and quality of life of older people.
- ◆ Development of innovations for prevention and care.

### **Extension of working life**

Although this chapter is concerned with old age, it should also be kept in mind that preventive measures should be taken at an early stage, *i.e.* after age 45 when people are still working. In most OECD countries, there is a trend towards retiring at a lower age. Facilitating the extension of working life will involve a broad package of policy measures, including an exploration of the policy implications of lifelong learning (OECD, 1996a). There is a need for standards setting, co-ordination and exchange of experience. Opportunities for continuing education, training schemes and open universities are needed as are improvements in the design of process technologies. Changes in human resources policies and in the organisation of work are necessary, as is a better balance between work and family life. Another well-documented problem

is discrimination on the basis of age or disability. Preventing loss of function at work is a further challenge. Action against ageism in the workplace also creates a need for increased research.

In Finland, the National Age Programme is a set of nation-wide activities intended to improve the situation by organising information campaigns, education and experimental and developmental projects. Three years after the start of the programme, there have been changes in statistics on the length of working life.

## **Improving the accessibility to the environment and the activity, mobility and quality of life of older people**

### ***Accessibility to the social, cultural and physical environments***

An estimated 12% of the European Union population suffer from some disability. As the needs of this population are neither very visible nor very recognised, one can justifiably speak of “forgotten consumers” (Roe, 1995).

The UN Standard Rules highlight an area that is especially important for equal opportunities: accessibility is one of the target areas for securing equal participation. It is defined to include two elements: *i*) access to the physical environment; and *ii*) access to information and means of communication. According to the Standard Rules, it is the responsibility of states to take appropriate action to remove obstacles. Persons with disabilities and their organisations should play active roles as partners in this process.

### ***Activity, mobility and quality of life***

The social, institutional and organisational contexts of activity are very important for quality of life. In modern industrialised societies, the active participation of older people and persons with disabilities in social relationships, cultural events, services and in all types of activities outside their homes is made difficult through the loss of physical abilities, often associated with a chronic illness. Such difficulties are exacerbated by unfavourable environmental and technological conditions. People may not even feel safe in public spaces. Mobility and housing, transport and home technologies are potential areas for major innovation.

Policies and technologies are needed to prevent loss of function due to age or disability (Harrington and Harrington, 2000). “Sufficient” physical condition is a prerequisite for people to manage on their own and consequently for keeping a check on the resources spent on care. Exercise is good for people of all ages, and mobility is one of the most crucial dimensions of an independent life. At the same time, the transport infrastructure should address the needs of this population.

Since disability is relative to the environment, special attention should be paid to creating adaptable environments. The environment imposes limitations on the mobility of much of the population (families with children, older people, people with disabilities or illnesses), and their demand for services can be met through appropriate planning of the environment.

“Design for all” is a concept that aims at creating environments that can be used by persons with disabilities (Hyppönen, 2000). It uses high technology to meet people’s needs through adaptable, “smart” homes. When the environment, furniture and rooms are designed to meet



individuals' specific requirements, even a person with serious handicaps may be able to live alone. For an ageing person, a dwelling adapted to his or her needs is a prerequisite for independent living.

Such technology should be exploited as extensively as possible. In Finland, the town of Joensuu, for instance, has built a suburb of 3 000 inhabitants, which is accessible to all and in which a considerable proportion of the dwellings are of the "smart" type. The electrical installation work has been designed so as to allow for necessary appliances to be fitted whenever the need arises.

A survey commissioned by the EU Housing Ministers revealed that most older people in the EU live in mainstream housing (European Union, 1999). In some countries, senior citizens are generally independent, while in others most live with relatives. The survey indicated that there are various intermediate forms of care in addition to institutional care and living at home in every EU member state. As a whole, institutional housing is quite unusual in the EU. The survey also showed clear differences among member states in housing policy goals and measures.

This issue has also been explored in many OECD reports and seminars, recently in Oslo in 2000. A major change in OECD countries has been the evolution of family patterns towards nuclear families and greater intergenerational independence. As a result, the proportion of solitary households has risen and is still increasing steadily. Traditionally, figures have been high in the Nordic countries, but they are also on the increase in Austria, Belgium and the United Kingdom. In southern Europe the proportion is lower but also increasing. In Japan only one out of seven older persons today lives alone; culturally, an increase in the number of people living alone might be a great challenge. Housing for older people or people with disabilities is not simply a question of housing policy; it is important to ensure that all solutions are part of integrated strategies that incorporate, as appropriate, housing, transport, health and other services.

### **Can global standards be established?**

Standardisation might be very important for recognising the needs of older people. Standardisation is, however, a very slow and detailed process. To address the needs of older persons and people with disabilities, a draft of ISO guidelines for standardisation is currently under discussion worldwide (Draft ISO/IEC Guide 71, 2001).

### **Development of innovations for prevention and care**

Various population surveys have shown the value that is attached to health. Maintaining the abilities of older people by preventing threats to health, even challenging the ageing process itself, should be of primary concern. It is essential to develop strategies for prevention and early diagnosis that are based on understanding the processes of ageing from a physiological as well as social perspective. Promotion of health is a great policy challenge and biotechnological research may play a role in this area.

Older persons and persons with disabilities should be given all the support they need to maintain their abilities and to develop their coping skills. Combating disability and promoting supportive technologies is most important (Ohlin *et al.*, 1995), yet the development and use of these technologies are quite limited in most OECD countries (ECE, 1995). There are many reasons for this: lack of information, lack of proper standardisation, paucity of enterprises in this

area and lack of interest by major companies. Gerontechnology, a new field of technology for ageing people (Harrington and Harrington, 2000), is being developed, and many OECD countries have achieved good results. However, in the European Union, the process seems to be rather slow and the relevant R&D units are too small and dispersed to generate significant breakthroughs.

The well-being of older people and of persons with disabilities depends on the close interplay between scientific achievements, industrial applications, social organisation and information flows – all provided by distinct categories of professional actors and agencies – and also on intermediaries, families and relatives. Telematics will offer new opportunities for organising care services for older people and persons with disabilities. Another innovative trend is to merge health and social services into seamless care provision: a person-centred integration of prevention, welfare improvement and health care. The development of modern services reflects the trend towards increased home services in all industrialised countries, with concepts like virtual hospitals and wide application of telemedicine. Technological solutions that support self-help among older people and people with disabilities have been largely neglected. Systematic, user-centred development work which allows full involvement of both older people and people with disabilities will produce the best systems and service applications.

Caregivers also need help from technology. Health, rehabilitation and social welfare services are highly labour-intensive, and personnel costs represent a significant portion of total expenditure. Appropriate technology would help them in their tasks, but is rarely available. More attention should also be paid to ergonomics. Lifting, pushing, washing, dressing, etc., are tasks to be done gently yet firmly while not burdening the back and limbs of the caregiver.

Several major EU and other European research projects and actions have tackled these issues. These include TIDE (Technological Innovations for the Elderly and Disabled), and COST A5, COST 219 and COST 219bis (von Tetzchner, 1991; Roe, 1995; Graafmans *et al.*, 1997). Further, an independent ETAN expert working group provided an analysis (1998) for the European Commission, and the EU's Fifth Framework Programme includes a key action named Ageing Populations and their Disabilities.

### **Evidence-based technologies?**

Rapid technological development provides an abundance of methods to prevent, diagnose and cure disease and ailments. Unfortunately, many of the new drugs, devices and other health technologies are more expensive than their predecessors. Another general problem with new technologies is that we often know too little about their actual effects on the life of individuals and on society in general, especially over time.

Evidence-based medicine raises confidence in medical treatment, which should not be based on expert opinions, assumptions or traditions, but on evidence produced in well-designed scientific trials. However, for the elderly, the principles of evidence-based medicine are too often hard to apply. Old people are usually excluded from randomised clinical trials, either because of age or because they have other diseases that exclude them. Thus, most of the scientific evidence on which the treatment of the elderly is based derives from studies carried out on younger patients. How well the results obtained in the young apply to the elderly is not known. Thus, current practices in medical research leave the patient group that suffers most from disease and consumes, per capita, the greatest amount of drugs, without a sound scientific basis for treatment.

Another cause for concern is prejudice or discrimination against the elderly. People of all ages should receive equal treatment, but older patients do not always receive the same treatment as younger patients, for example, for breast cancer and myocardial infarction. At the same time, it must be recognised that certain treatments and procedures may not be appropriate for the elderly, because of their lesser physiological reserves. However, the choice of treatment should be based on physiological and not chronological age.

Drug therapy and other health services provided to the elderly should be based on scientific evidence. Novel health technologies used for elderly patients should be rigorously assessed before they are used in everyday practice. New technologies have too often been based on feasibility and immediate effects. This is not sufficient. In addition to initial clinical effects, long-term effects and the economic, ethical, legal and social consequences of a given technology must be considered. Thus, the assessment of the effectiveness of health care should go beyond scientific evaluation of the effect on the disease.

Effective health technologies may differ greatly in terms of cost effectiveness. Decisions based on cost effectiveness should ensure that public health policies produce the maximum results for the financial resources available. This is a great challenge if equitable treatment is to be provided to all citizens despite individuals' differences in terms of economic resources. It is especially challenging to ensure that patient groups with limited ability to influence their own treatment, such as the elderly, are not deprived of effective therapy.

Patients themselves are usually not interested in the cost effectiveness of their treatments or other health services they use. What matters to them is whether "it works", *i.e.* whether their quality of life improves with treatment. Although there are models for estimating the impact of various treatments on the quality of patients' lives, we still know too little about individual preferences, *i.e.* whether treatments and other procedures provide the elderly with what they themselves want.

### **Technology is social**

It is a common misconception that technology is "ready and waiting" and that it just needs to be brought into more widespread use. Everyday technologies have various problems that are simply accepted. Technical appliances designed especially for older people and people with disabilities must be easy to use and have simple, easily understood operating instructions and they should be encouraged to use them. Our children are experienced with information technology while our parents are often ignorant of technical equipment and computers. This is not a law of nature but a problem to be solved by education.

What is needed is a new awareness of the social character of technology. All technology is social, and the social dimension of technology is very powerful (Nowotny, 1992). Technology needs people and people need technology but its application is acquired by training. Technology is evolving rapidly and one of the greatest challenges is its integration with accumulating experience and development of the necessary skills.

### **Integrated policies are needed**

There are obstacles to the promotion of active ageing, many of them political. National policies do not always consider the rights of special populations (OECD, 1996b). Active ageing

means decent economic opportunities to meet one's day-to-day needs. Too many older people and people with disabilities live in poverty. Many of the obstacles are societal: there are prejudices, misunderstandings, feelings of denial and even fear and shame. In many societies, ageing may be a difficult personal experience, especially for women. Too often ageing is seen as a barrier to full participation in life.

In many countries, public discussion and political debate on future development include serious concerns about the implications of providing care for larger numbers of disabled and/or frail older people. Public budgets and the viability of pension systems may marginalise them. Countries have to start analysing the challenges and obstacles, and then combat or remove these obstacles.

It is obvious that specific solutions for one population or another are not enough. Integrated approaches are needed, especially with regard to the ageing population. Most policy makers have recognised that political and administrative activities need to be integrated horizontally, taking into account the needs of ageing people. The policies to be integrated are numerous and involve technology, social issues, health, lifelong learning, gender and place of residence. This means that local policies and developments worldwide intersect. Co-operation is needed among public policies, global developments and private enterprises.

It is important for the OECD to take an active role in the discussions, as mandated by OECD Ministers. The OECD has organised several expert workshops on the topic and provided excellent background information. Several member countries have explored the ageing processes and their policy implications (OECD, 1998b). Long-term care and future pension systems have been discussed. In Japan, the new insurance system for the aged, "The Gold Plan", ensures the commitment of the local authorities where services are needed. Australia's Ageing Society (1994) explores the situation to the year 2051. Several other countries have begun a reorganisation of their health and social welfare systems (France, the United Kingdom, Denmark) or have thoroughly discussed how their pension systems should be modified (Ireland, Sweden).

## **Conclusion**

Biotechnology, gerontechnology, design-for-all technology and/or barrier-free physical and social environments will be developed when people's needs are taken seriously and the needs of these population groups are understood. However, they do not alone guarantee the well-being of older people, or remove the risk of social isolation and exclusion. It is necessary to combat poverty and to work to promote tolerance and equal opportunities for all. The further we get in ensuring equal political, economic, social and cultural opportunities for older people, the closer we can come to the ideal of full accessibility of user-friendly technologies, systems and services (Keskinen, 1999).

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## *Chapter 17*

### **STRATEGIES FOR AVOIDING ELDERLY EXCLUSION AND MISTREATMENT**

*by*

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A new policy agenda of the European Union to improve the lives of older people is emerging with regard to policy priorities and suggestions about legal structures. One priority, especially important to achieve healthy ageing, is the promotion of active, productive ageing. To do this, it is necessary to be consumer-centred and focused on the individual older person.

Older people are demanding and will demand equity of treatment with other groups in society, an idea perhaps more novel to Europeans than to Americans. Active healthy ageing is not an easy goal to achieve as it requires a consumer-centred policy and the involvement of older people in its planning. Obviously, a big barrier to achieving this goal is stereotyping and age discrimination. It is extraordinary that even in the United States, only employment is covered by anti-discrimination statutes. There are many barriers to the full participation of older people in the workplace. It is hard to recruit the elderly fairly and provide them with opportunities for training and retraining. Many feel that it is not worth the effort to recruit the elderly because they have not properly calculated the benefits of elderly employment.

In envisaging a longer life course, it is necessary to start thinking about abolishing retirement as we know it and look at what education and training will mean. With the long life spans now predicted, it is ridiculous to think that children will go to school at age three or four, be trained to work until they are only 50 or 55 years old, and live as many as 50 or 55 more years without a real purpose. Companies like IBM and Cisco Systems have introduced initiatives in many deprived areas to train young people in interactive learning. Such training should be geared to working people of all ages, using new technology and establishing continuing education throughout life. In Europe, there are encouraging signs that an end to some discriminatory practices is in sight as a result of human rights legislation and a new directive stating that age should be at least partially eliminated as a factor in employment. However, the many exceptions in the directive make it difficult to see total success.

The discussion of discrimination in employment is meant as a prelude to examining discrimination in health care, an area where perceptions of older people are often counter-productive. Discrimination, while often not intentional, results from values held by the majority in the community. Such societal values are clearest when health care is to be rationed. All countries have some system of rationing. However, systems should be transparent so that individuals know whether they face an equitable situation. In the United Kingdom, rationing

usually takes the form of waiting lists, which are particularly damaging to older people who have less time to wait. Rationing can also be related to the availability of specific services in different parts of the United Kingdom. This so-called "postcode rationing" is still prevalent.

Age discrimination is evident in many areas, including interventions in heart disease, in end-stage renal disease and in screening for breast cancer. For breast cancer, discrimination carries unintended consequences. Older women do not have the same response to denial of breast cancer screening. Although they are legally entitled to screening, many older women believe that they cannot get breast cancer. In a survey carried out last year, one in 20 persons aged 60 and older said that they were refused treatment in the National Health Service in the United Kingdom, and one in ten 50 years and older said that they experienced some sort of discrimination when they sought health treatment. Clearly, the phenomenon is widespread. In another survey, general practitioners interviewed agreed that there was discrimination in health services. Discrimination may be unintentional but it happens in the United Kingdom and probably in other countries.

The system of medical care should be transparent, regardless of how it is rationed. Rationing might be done through consultations with local population groups. My own view is that it must be based on individual clinical assessment of need, with age as a criterion for prognosis, but not a decisive factor limiting clinical intervention. This will become more necessary as older people become more empowered, a process that has begun and is happening very fast in many countries. As groups become empowered, they may fight for an issue and quite easily influence policy. They can influence whether a form of treatment is deemed cost-effective or not acceptable. That is real power.

Older people now have enormous consumer power, but even more importantly they have voting power. In 20 years, more than half of the voters in the United Kingdom, will be over 50. Even today in many political constituencies approximately half of voters are aged 60 to 65. Older populations are vocal, enthusiastic voters. Politicians are very much aware of this, and the government recently had to make big financial concessions to older people, and the British elderly have seen their pensions and other benefits raised, although this was contrary to the declared policy of the government.

Another example of patient power influencing policy is the reversal of a decision taken by the National Institute for Clinical Excellence (NICE), a body that determines whether a new drug is cost-effective and should be distributed by the National Health Service. The drug under consideration was beta-interferon, used in the treatment of patients with multiple sclerosis (MS). The NICE, which makes recommendations to the government, decided that it was not sufficiently cost-effective for introduction throughout the National Health Service, although it had already been distributed to patients suffering from the disease. This conclusion was widely disseminated to individuals with MS and patient power forced the government to rethink its policy on this particular drug.

Despite such evidence of empowerment, older people still very often receive a lesser service from less qualified people, particularly in the social services, especially in comparison to what children receive. Not only is this discriminatory, it can be dangerous. Where there is neglect, people can directly or indirectly abuse older people. Advocacy has to generate greater awareness of the fact that abuse of the elderly exists in all socio-economic classes. The Americans learned this a long time ago, but the British are also recognising it. Enhancing patient advocacy and public awareness is very important for promoting healthy and active ageing.



Many financial challenges must be addressed. Providers of financial services are sometimes guilty of age discrimination. Older people have enormous difficulty getting insurance if they want to drive, if they want to hire a car, if they want to have health insurance, or if they want to volunteer. These problems could be solved in most cases by testing ability or capacity. Does the older adult have fast reactions, good eyesight, driving skills or competence as a volunteer? Objective criteria should be used. There is no real reason for age to be the sole factor in the decision.

Life insurance presents enormous challenges for the elderly. The United Kingdom is the first country to have given life insurance companies the right to know if genetic testing shows a hereditary condition called Huntington's Chorea. Although this is the first disease to be classified under the "right to know" by insurance companies, others will no doubt follow. It could be argued that what needs to be done is to pool risk. But the problem appears to lie elsewhere, because if there is genetic certainty or near-certainty that someone will get a disease, the issue is not one of insurance at all but of compensation. Insurance is about risk assessment and where genetic results give virtual certainty there is virtually no risk. Perhaps what is needed is a governmental programme to compensate victims and their families for the near-certainty of a dreadful disease.

Of course, in a different setting, the same applies to stem-cell research. It is very important to generate public awareness about the benefits or the potential benefits of this research. If stem-cell therapy proves as successful as hoped, it will provide cures for many tragic diseases. A social consensus is needed before opposition to such research overwhelms the common good it provides. Therefore, dissemination and translation of research findings are absolutely essential if the public is to understand, support and ultimately benefit from the research effort.

Although age in itself must become less relevant in individual cases, enhancing specialist knowledge of ageing is important. Not only is specialist medical care essential, but every physician should have knowledge of geriatric care. Medical education should provide a life-course approach to all patients, as part of the training of physicians and other health professionals. Governments must look at ways to measure success in terms of health interventions if disease prevention is to be a priority. Public health must become as important as cure and treatment, and the effectiveness of health-care systems and interventions must be continually assessed and evaluated. All governments must measure the success of their health systems. For therapeutic interventions, one, two or three years may suffice, but for preventive interventions evaluation is needed over a longer period.

Thus there is much to be done to make active and healthy ageing a reality. Older people have to be full citizens in society – that is the priority for all of us. Biotechnology and ageing research now being carried out are, quite possibly, the key to achieving this better health for the elderly.

## *Chapter 18*

### **BARRIERS TO THE IMPLEMENTATION OF ADVANCED TECHNOLOGIES IN CLINICAL PRACTICE AND CARE FOR THE ELDERLY**

*by*

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Ageing and old age can have many manifestations. One can stay alive and healthy like Frenchwoman Jeanne Calment who died at 122, or one can be overburdened with disease, particularly cognitive impairments, and be bed-bound, malnourished and incontinent. For elderly patients in such situations, technology has something to offer. Technology provides powerful tools to physicians. Not only can it improve our diagnosis and treatment of disease, it can also improve preventive measures and decrease disabilities. These advances can manifest themselves at the societal level, improving the health of whole populations and enhancing the quality of life of senior citizens. But technology can also decrease the burden of caring for an individual and reduce the costs incurred as well. Why, then, is there a reluctance to use technology effectively in relation to elderly people? Why are diseases often not diagnosed early enough? Why are some medical procedures underused or misused, and why have older people often received services by chance more than by need? It is worth exploring the barriers to the development, use and dissemination of technologies old and new.

#### **Stereotyping the old as poor candidates for technological intervention**

The elderly are too often considered poor candidates for technological interventions. Old age is still wrongly perceived as synonymous with poor health, physical disability and cognitive impairment. That view persists despite epidemiological studies in some countries showing an increasing number of healthy elderly people with fewer and fewer disabilities. There is also a great fear that elderly patients will pose a higher risk of complications and reap fewer benefits from treatments than young patients. However, much scientific evidence indicates that the elderly are good candidates for most procedures and current therapies and their outcomes will not necessarily be worse. Co-morbidity and other factors are more important than age itself.

How can these stereotypes be overcome? The first step would be to increase practitioners' knowledge of treatment possibilities, not just among specialists in geriatrics but also among physicians in all specialities. Medical and nursing students should also be taught the basic principles of geriatric medicine. The use of evidence-based medicine would of course play an important role as well. Greater

inclusion of the elderly in clinical trials would be an important way of gathering scientific evidence of the possibilities for elderly care.

### **Government resistance to investing in the elderly**

It is also widely believed that the elderly are a less good health investment than the young, and that investments in elderly care is a misappropriation of money better spent on other groups. The argument is most frequently heard in countries facing serious financial constraints, for example in eastern and central Europe and developing countries. This is not only inaccurate but harmful. Investment in prevention and treatment of diseases in old age can reap rewards by lowering morbidity, decreasing disability rates, reducing the burden of care both for formal and informal (family) care, and it can promote the active participation of the elderly in the market and workforce.

Per capita costs of health care vary significantly among countries. It would make a great difference if disability is decreased or disease postponed. Increased government spending for health care for the elderly could have both medical and financial impacts by changing the distribution of elderly disability and onset of disease. Moreover, delaying the onset of disease and disability would yield broad social benefits.

In the Czech Republic, elderly patients are the most fragile group. Health-care spending at higher ages has increased dramatically in the last decade. Unfortunately, the increases have not been accompanied by a decrease in disability or by the postponement of disease, as in some western European countries. Rather, they leave elderly vulnerable to the rationing of health services.

### **Fear of the high costs of new technologies in health care for the old**

High technology is what most people think of when the word "technology" is mentioned. Low technologies, such as those used in rehabilitation and nursing care (often for serving the geriatric population) have been rather neglected. Moreover, new low technologies have not been introduced as extensively as acute care and "heroic" medicine.

Use of advanced technologies and their associated improved outcomes create high expectations and demands in society. In the Czech Republic, the use of dialysis increased by 300% and coronary bypass surgery by 500% in a ten-year period. Elderly patients are more frequently being offered advanced technologies, procedures and drugs from which they can benefit.

Is it possible to find acceptable ways to limit the use of technology and to set priorities for their application? This would require more realistic expectations and efforts to develop evidence-based medical guidelines for treatment of disease in different age groups. The aim would be to develop affordable and economically sustainable health care. The European Union seeks to develop policies for technology development that will properly balance the biomedical and socio-economic approach. Biomedical research is important. Japan spends 3.1% of its gross domestic product on biomedical research, the United States 2.7% and EU countries 1.8%, while eastern European countries generally spend only 0.4% to 0.8%. This will have to change if technological development is to be put to good use everywhere.

### **Improper dependence of elderly persons on medical guidance and assistance**

A high level of autonomy among elderly persons is generally accepted in developed countries but not in some Mediterranean, central and eastern European countries. In eastern Europe, for example, a

high level of state paternalism is a legacy of the communist years. There is also an asymmetry in the doctor-patient relationship, with doctors dominating and engaging in little dialogue with patients. This means that in the use of new technologies, some countries will rely more on the recommendations of governments and doctors than on the judgement of patients.

Helping the elderly become more informed consumers will require both education and a wider social debate about the proper goals of medicine at all ages. Medicine and health are a means to a comfortable human life, not an end in themselves. Bioethics will play an important role in this debate, and perhaps more surprisingly, so will information technology. E-mail is already helping many elderly people overcome loneliness and is having a much greater influence than could have been imagined even a few years ago. The support of autonomy and personal responsibility of the elderly for their own health is important in creating informed demand for medical technologies and for achieving healthy ageing in society as a whole.

## *Chapter 19*

### **DISSEMINATION AND USE OF NEW TECHNOLOGIES THROUGH TELEMEDICINE FOR ELDERLY PEOPLE**

*by*

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Human longevity and hence the elderly population are rapidly increasing. In 1900, there were 30 million persons over 65 years of age in the world. In 2000, there are more than ten times this number (350 million) and there could be 50 times this number by 2050. In Europe and Japan, 20% of the population is over 65. More striking is the changing balance in the population of the European Union. There will be 10 million people under 20 years of age compared to 40 million retirees over 60 years of age.

Furthermore, within the next two decades, there will be a change in the profile of the elderly population. Thanks partly to progress in biomedical research and decreasing mortality of individuals over 60, by 2020 there will be a new generation of elderly people with a lower percentage of disabled individuals and a higher percentage of active elderly. In addition, according to the Dutch Social and Cultural Planning Bureau, the elderly in developed countries will be more highly educated and less dependent than the elderly of today.<sup>8</sup>

For these reasons, ageing presents a major opportunity for the European economy, especially for those OECD countries that develop innovative technological and organisational solutions to the social and economic needs of an ageing population. Technology will play a crucial role in these developments and the social dimension of technology must also be kept in mind.

At present there are two discrete aspects to technology in gerontology which are extremely promising:

- ♦ Biomedical research, which is presently focused on the identification of geronto-genes based on genomic and proteomic analysis, will also tackle other scientific questions such as: damage by free radicals, telomere shortening, repair of DNA damage and immortalisation of cell lines. Furthermore, the areas of regenerative medicine, embryonic, foetal or adult stem-cell technologies hold considerable promise.
- ♦ Information technology appears to offer major breakthroughs, as the Internet can be used to transmit via ground or satellite links data collected by electronic medical devices. This

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8. Timmermans, J.M. and M.M.Y. de Klerk (1996), *Report on the Elderly*, Sociaal en Cultureel Planbureau, Cahier 135, the Netherlands.

technology can be applied to blood pressure, temperature, registration, imaging techniques including echography and remote sensing devices.

This following discussion examines how the elderly and disabled can benefit from information technologies and offers proposals for a fresh approach to integrating active elderly people in the new information society.

Telemedicine is a vital part of the e-health initiative and, in part, addresses the management of personal data flow for diagnostic, therapeutic and/or preventive purposes. Tele-imaging and remote-sensing technology can provide data on elderly people using minimally or non-invasive methods. There are now prototypes of medical devices smaller than a grain of rice.

Biosensors can be developed to monitor blood glucose levels, incontinence, cancer evolution and inflammatory activity. Space technology allows the transmission of echographic, electrocardiographic and respiratory data, which can help alert physicians to the risk of heart attack, stroke or asthmatic crisis. Telemedicine can potentially allow new technologies to benefit all elderly people, whether disabled or active.

Transmission of medical data by satellite, for example, can be used in emergency situations such as earthquakes, floods or even traffic accidents, where elderly people are especially vulnerable. When necessary, emergency evacuation by boat or plane could be facilitated using these systems

Prevention can be facilitated by the transmission of medical data at collective level as well. Transmission of epidemiological data on diseases more specific to elderly people, such as cancer, neurodegenerative disorders (Parkinson's or Alzheimer's disease), chronic arthritis and bronchitis should allow follow-up on a regional or even global level.

Remote sensing will make it possible to improve surveillance of elderly patients, thereby avoiding needless transport and contributing to home-based care. Use of satellite positioning systems to monitor and locate disoriented, mentally ill or elderly people could greatly help their families. Such technologies will not eliminate the face-to-face relationship between elderly patients and health-care professionals. In fact, contacts can be even more frequent through telemedicine. But monitoring will allow the elderly to continue to live in remote parts of the country in their own, familiar, surroundings. As home-based care develops, the number of jobs for health-care professionals and new services and opportunities for enterprises in the community can be expected to increase. Telemedicine will allow communication of medical data from the home to clinics and/or hospitals. With this kind of secure grounding, the elderly and disabled will have a chance to maintain and expand their participation in social life. Indeed, the use of information technology in health care should not be seen as a risk of further isolation, but rather as a means of achieving better security for the Internet generation as it grows older. Subsequently, increasing the independence of elderly people may create more need for services based on information and communications technology (ICT).

In the use and development of these technologies, it is necessary for both society in general and the individual to take a holistic approach towards ageing. This will require the right balance between an individual's right to privacy and confidentiality and the proper use of information by stakeholders. Smart cards with personal confidential codes might be sufficient for this purposes.

In conclusion, e-health offers great potential to contribute to the health and quality of life of elderly people, and international co-operation could facilitate progress towards this goal. A new vision for ageing policy is necessary, one that would encourage the virtuous circle between technological development and socio-economic development. According to Professor Chihiro Watanabe of the

Tokyo Institute of Technology: "Today, the main challenges are to improve assimilation capacity, build stronger linkages between university and industry, encourage information technology diffusion and capture the momentum of the digital revolution." These challenges merit a new vision. One of the major challenges for the EU, in partnership with different OECD countries, is to deliver on this vision and specifically to help developing countries and elderly people living in remote geographical areas.

In recognition of the growing importance of ageing in OECD countries, and in order to encourage a fuller involvement of elderly people in the new information society, OECD countries should improve "e-health for the elderly" by improving the quality of electronic information, and the respect of the individual (protection of confidentiality and lifestyle) and ensuring cost regulation. Information technology has the potential to contribute greatly to the World Health Organization's definition of health as "a state of complete physical, mental, social and spiritual well-being, and not merely the absence of disease."<sup>9</sup>

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9. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 states (Official Records of the World Health Organization, No. 2, p. 100) and entered into force on 7 April 1948.

## *Chapter 20*

### **GOVERNMENT SCIENCE AND HEALTH POLICY STRATEGIES IN JAPAN**

*by*

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This chapter focuses on cancer as an example of a disease related to lifestyle which affects the elderly population. It begins with a quick look at the cancer population figures in Japan and how the country is tackling this problem using new technologies. It then describes the life science policy decision-making process of the Ministry of Health and Welfare in Japan. There is a brief description of the Millennium Project, launched in 2000, and the Medical Frontier Programme. Finally, barriers to the application of exciting achievements in the life sciences to future daily health care are considered.

Cancer is the leading cause of death in Japan, affecting one out of every three people over the course of their lifetime. In a given year, about half a million people suffer from the disease and 300 000 perish. The cancer mortality rates are presently increasing despite the fact that cancer cure rates have improved. About 80% of people with stomach cancer can now expect to survive another five years. The cure rates for liver and lung cancer are also improving. An estimated 2 million Japanese have survived a first cancer treatment. Survivors should not automatically be categorised as "disabled persons". While some in fact are disabled, this is not recognised by the government.

Obviously the purpose of cancer control is to decrease the number of cancer deaths. "Control" relates to cure rates, which are improved by secondary prevention, early diagnosis and early treatment. It is clearly important to pursue primary prevention of cancer, as well as treatment that yields better results, in other words treatment which leaves the patient free of disability.

Progress toward these objectives has received a boost from advances in two new technologies. The first is computer science, which has developed over the past 20 to 30 years. Computer science has had a very strong impact on daily life and on medical care. Imaging, endoscopic surgery and patient-friendly treatment, as well as technology and information transfer, have all advanced because of progress in computer science.

Another application of the technology is just beginning to enter the clinical world. Remarkable discoveries made in the laboratory on an almost daily basis are being put to practical use more and more rapidly, and the prospects are indeed exciting. Take, for example, the power of imaging. Four or five years ago, to have a three-dimensional display of lung cancer it was necessary to have a supercomputer, but now all that is needed is a regular computer. Such imaging admittedly may not be put to daily use, but if there is a cancer that cannot be detected by regular helical CT, it will show up with this kind of three-dimensional display.



There are 28 regional cancer centres throughout Japan; 16 of them are equipped with telemedicine or video-medicine facilities, and medical conferences are held regularly. These also are possible because of advances in information and computer technology. In addition, up-to-date information about cancer is available to the general public on a Web site. Also, in collaboration with the Ministry of Telecommunication, there is a videoconference link via satellite with the Gustave Roussy Institute in France; at this time it is only used for basic science, but it will probably prove useful later for clinical science.

Archiving information on cancer requires computer memory and space. Imaging improves the diagnosis and efficacy of cancer treatment. Establishing criteria within a global cancer information network is thus very important for assessing the efficacy of medical care throughout the world. Japan's National Cancer Center houses the Secretariat of the G7 Medical Image Reference Center Project. Participating image-collecting reference centres submit images to the reference database. Making images of cancer available over the Internet facilitates provision of quality and cost-effective health-care delivery and contributes to the health and welfare of the world community. The project has gathered and stored all the typical cancer cases in images in an effort to arrive at some sort of standardisation for diagnosis.

Turning to primary prevention, very routine improvements in lifestyle can be important to the prevention and treatment of infection. An estimated 20% of cancers can be linked to infections: liver cancer to hepatitis C virus, cervical cancer to the papilloma virus and stomach cancers to *Helicobacter pylori*. As chemoprevention is still in clinical trials, it is difficult to say how it will be incorporated into daily life to prevent cancers. Prevention based on genetic predisposition is also relatively new. The entire DNA sequence of the human genome is now known. With this information at hand, predictive medicine treatments tailored to individual genetic characteristics will be possible. These advances, whose value in terms of health-care costs are difficult to estimate, will certainly favour primary prevention of cancer.

The lifestyle factor is difficult to quantify, but there are significant differences in the incidence of different types of cancer between countries. In the United States, for instance, lung cancer is most prevalent, while in Japan stomach and lung cancer are most prevalent. Japanese immigrants to California or Hawaii have almost the same incidence of different cancers as Caucasians in the United States, demonstrating that environmental factors or lifestyle have a greater influence on cancer incidence as a whole than genetics. In hereditary cancer, a single cancer-causing gene mutation occurs, but for most common cancers multiple genetic and environmental factors have been implicated.

The Ministry of Health and Welfare in Japan has a procedure for developing strategies for health science research. In the author's opinion, the Medical Science Committee plays the most decisive role. In this committee, lay persons from consumer groups, investigators from academia, industry and the social sciences make recommendations to the ministry. The ministry decides whether to take up the recommendation and the Finance Ministry decides whether to allocate money for the recommended research.

Action needs to be taken on behalf of the elderly. The Millennium Project, initiated by the Prime Minister, considers the life sciences as one of the priority fields of science. A relatively large sum of research money has been allocated to this field. Especially important for the elderly are the human genome studies related to Alzheimer's disease, cancer, diabetes, hypertension and asthma. A large amount of money is also going to the field of regenerative medicine, especially as it relates to stem-cell therapy.

The Medical Frontier Programme deals with basic science and clinical science. The basic sciences in the post-genomic era will include proteomics and medical electronics. In this programme, clinical trials will contribute importantly to the development of evidence-based medicine. Japan should have more investigator-initiated than industry-initiated clinical trials. Emergency medicine training is also included in this Medical Frontier Programme.

The life sciences must address human welfare, as well as matters of health, and thus must address issues in economics, ethics and medical engineering. The links between these various disciplines should be strengthened and industry must be involved. We should have strong governmental regulation and evaluation of the safety and efficacy of medical products coupled with free market competition for health care and products. While safety is often considered to be priceless, health care is necessary for safety, but it is costly.

High costs are obviously an important barrier to the application of new biotechnologies, often owing to patent protection. However, it is not very well understood how patents influence costs of products or how those costs are eventually influenced by the market. Also, while technology is complex, it should become user-friendly and increasingly automated. People can use telephones and computers without understanding their mechanics. Therefore, the complexity of a new technology should not be a big barrier to its eventual use and dissemination.

Finally, Japan should have stronger infrastructures. Social consensus is very important in Japan. Although the word "ethics" is avoided, social consensus is needed to use a technology like genetic diagnosis or prenatal care of the foetus. It may be that obtaining social consensus will be the most important element permitting the application of costly and complex technologies that can serve to improve the health of the elderly population.

## *Chapter 21*

### **LONG-TERM CARE INSURANCE IN GERMANY**

*by*

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Until 1995, German residents requiring permanent care did not receive adequate help. Instead, they became dependent on social welfare with all the negative consequences of a means-tested welfare scheme. In May 1994, however, the German Federal Parliament passed a new social insurance programme to meet the needs for long-term or permanent non-medical care. The Long-term Care Insurance (LTCI) Act came into effect in three stages between January 1995 and July 1996. This programme has closed the gap in Europe's oldest social security system inaugurated by Bismarck in the 1880s.

#### **The scope of the problem**

A few numbers illustrate the magnitude of the problem. Today in Germany, 1.86 million people, roughly 2% of the total population of 82 million, need permanent (non-medical) care. About 550 000 people live in nursing homes and the remaining 1.3 million are cared for at home by relatives, neighbours, friends, other volunteers or professional caregivers. By legal definition, people in need of permanent (long-term) care are persons who, as a result of illness or disability, require permanent assistance in coping with daily activities such as personal hygiene, nutrition, mobility and housekeeping. Although the definition covers people of all ages, the vast majority (approximately 1.5 million) are over 60 years of age, and 850 000 are over 80.

While the number of people requiring long-term care is increasing, the length of stay in care facilities has been steadily decreasing, from over five years a decade ago to less than two years today. The average age at which individuals enter a nursing home is approaching 85 years. About 70% of persons requiring nursing-home care suffer from dementia and most suffer from Alzheimer's disease. In addition, approximately half a million receive home care.

#### ***Cost of care***

Long-term care is costly and institutional care has become very expensive in Germany. The monthly cost for a nursing home resident is between EUR 1 524 and EUR 4 134, well beyond the means of persons with an average pension. Before the new care insurance scheme was introduced in 1995, the high cost of institutional care took the entire income of an elderly person regardless of the amount of pension received. In many cases, it led to the loss of personal wealth and a decline in the

standard of living, not only for those directly affected but also for the children or relatives of the individual requiring care. As a result, the vast majority of residents in nursing homes depended on "social assistance" to cover their monthly care fees.

Social assistance is a means-tested public welfare scheme. If a person is unable to pay for the nursing home, the local authority will pay the costs but may recoup at least part of its expenditure by recovering assets from the nursing home resident.

Family members look after approximately 90% of persons in home care. However, owing to social developments, family care is facing increasing pressures:

- ◆ People remain single or live alone after divorce or death of a spouse.
- ◆ Lower birth rates have resulted in fewer children available to care for their parents.
- ◆ Longer lifespan, with the result that children care for both their parents and their spouses.
- ◆ Professional situations, such that individuals who work full-time do not have the time to care for a relative.
- ◆ Distance, as family members may live too far away to help.
- ◆ Lack of insurance for individuals who provide home care for relatives but who are not in paid employment and have no adequate social insurance of their own.

### **The new care insurance programme**

The 1994 Long-term Care Insurance Act recognised that long-term care has become one of life's greatest risks. The main points of the new scheme, now fully operational, include comprehensive coverage for all persons employed in Germany and in need of permanent (non-medical) care, independent of nationality. It is a compulsory system that incorporates long-term care insurance as part of health insurance. Certain groups can opt out if they can obtain coverage through private care insurance.

The new scheme is financed by a "pay-as-you-go system" with income-related contributions, paid equally by employers and employees, including present pensioners and persons receiving care. Non-employed spouses and children are covered without paying contributions. The rate – at present 1.7% of "insurable" earnings – was fixed by Parliament. The new care insurance is being implemented by the health insurance funds through their nation-wide office network. No new administrative organisation was required, and full advantage was taken of the health insurance funds' existing expertise in health services.

Long-term care insurance is not a fully comprehensive scheme. It only provides partial coverage for people requiring care, with limited though generous benefits. As a general rule, home care is preferred to institutional care. The new scheme focuses on providing benefits that improve conditions for home care and relieve the burden on caregivers. Prevention and rehabilitation are given priority. The health insurance funds are committed to increasing their efforts to avoid or reduce the risk of requiring care by using medical prevention and rehabilitation. Rehabilitation continues during long-term care. Beneficiaries may choose freely between Germany's 8 600 nursing homes and over 12 000 home-care agencies. Their insurance funds must provide advice to allow an educated choice among care options.

Persons covered by LTCI are entitled to all the benefits and services the system provides should the need for long-term care arise, including personal services such as hygiene, nutrition, mobility and housekeeping. Assistance is aimed at helping the beneficiaries perform or regain the ability to perform these tasks on their own. On the basis of a professional assessment, beneficiaries are assigned to one of three care levels according to the severity of their needs. If a person applies for care benefits, a qualified nurse or a physician (from the medical division of the health insurance funds) will visit the applicant at home to determine whether and to what extent he or she will need long-term care.

There are eight options for long-term benefits, including home care, stand-in care, part-time care, short-term care, technical aids, nursing care courses for relatives and volunteer caregivers, social security insurance for informal caregivers and permanent institutional care. All but the last are aimed at strengthening home care in preference to institutional care.

### ***Home-care benefits***

People requiring home care may choose between benefits in cash or in kind. Cash benefit or home-care allowance is paid directly to the beneficiary. The amount depends on the care level of the beneficiary. It is only granted if the beneficiary is able to secure adequate home care through relatives, friends or neighbours. If the beneficiary chooses professional home care, the programme provides for home visits by professional nursing staff. In this case, the nursing benefits are paid directly to the home care agency providing the service. The nursing benefit is higher than the cash benefit.

In the years since the home-care benefits were established in April 1995, 67% of all beneficiaries have chosen the lower cash benefits over the much higher non-cash benefits. Although the number of beneficiaries turning to professional help is slowly increasing, data show that the family still is, and will remain for some time, the preferred form of care. Stand-in care ("holiday" care) permits relatives, friends, neighbours or other informal home caregivers to take a four-week holiday a year, during which the care insurance will pay for professional home care.

Part-time care in a day or night centre has to be granted if a person in need of long-term care is unable to obtain adequate help at home. The amount of benefit is again scaled according to the care level of the beneficiary. If home care or part-time care does not suffice, the beneficiary is entitled to care in a short-term facility. Short-term care can be granted for up to four weeks a year.

In order to facilitate long-term care, persons requiring care are entitled to nursing aids such as special beds. In addition, grants are available for adapting the normal home to the special needs of care (lifts, steps, bathrooms, etc.). The LTCI funds are obliged to offer free nursing care courses for relatives and other informal caregivers. Relatives, friends or neighbours performing informal, non-professional home care on a regular basis are now included in the German pension and insurance schemes.

In 1999, the LTCI funds transferred more than EUR 1 billion to the pension funds, providing cover for almost 600 000 informal caregivers. In addition, informal caregivers are entitled to paid training if they want to return to gainful employment after they have finished providing care.

### ***Permanent institutional care***

As mentioned above, approximately 550 000 people are cared for permanently in nursing homes. The LTCI funds pay only for care-related services including basic, social and medically related care.

The monthly care rate is paid directly to the nursing home. The amount depends on the care level of the beneficiary. As with home care, the beneficiary is responsible for paying for his or her living and accommodation, normally at a flat rate which is the same for all people living in the nursing home. If a beneficiary is unable to pay for the residual costs (either of care or of living and accommodation), the social assistance office will step in to pay the difference. Everyone in need is entitled to social assistance. However, as mentioned, social assistance is means-tested.

### ***Evaluation***

After five years, it is fair to say that the new long-term care insurance system has established itself as a major pillar of the German social security system, and is generally accepted by people in all walks of life. Surveys show that over 80% of the population appreciate the home-care arrangements and almost 65% of people questioned said that they regarded the new programme as an incentive to take on care for relatives and friends. In addition, families, neighbours and friends already engaged in informal care perceive that the home-care allowance is an important recognition of their work.

As far as institutional care is concerned, the public response is less clear-cut. In particular, it is felt that LTCI is not comprehensive, as it provides only partial coverage. Although dependency on means-tested welfare has virtually been cut in half, there is still a considerable minority of people living in nursing homes who continue to depend, at least partially, on social assistance.

A positive effect is that waiting lists for a place in a nursing home have by and large disappeared. This is mainly due to the emphasis on home care, combined with the fact that the new scheme has created an open, competitive market for care providers. Over the past eight years the number of nursing homes has doubled from around 4 300, in 1992, to 8 600, and the number of home-care agencies has risen from an estimated 4 000, in 1992, to almost 13 000. The impact on employment has been substantial. In the area of home care, the new LTCI scheme has generated more than 80 000 new jobs. Employment in institutional care is also rising, although no reliable data are as yet available.

Last but not least, the new scheme is solidly financed, as shown by an accumulated surplus of over EUR 5 billion. There are at present slight imbalances. For the next three years care expenditure will exceed revenue generated from contributions. This is mainly due to demographic and economic factors, but all figures indicate that after 2004 revenue will again exceed expenditure.

### ***Reform plans***

The Federal Ministry of Health plans improvements to the LTCI via two proposed bills. The first aims at improving the quality of long-term care and strengthening the rights of people in need of care, who are viewed as consumers in the "care market". The second aims to improve the care of people suffering from dementia. The government regards the Dementia Care Bill as a first step in tackling the problem of dementia on a broader scale.

### ***Dementia Care Bill***

The proportion of old people in almost all OECD member countries has risen considerably, and will continue to rise in both absolute and relative terms. It is estimated that by 2030, one in three people in Germany will be over the age of 60. As populations in OECD countries grow older, the incidence of both dependency and dementia will rise. As a result, the need for care for dementia is

shifting towards patients at higher ages. The majority of these patients will have Alzheimer's disease, but the number of patients with vascular dementia will also rise. Given the state of present medical knowledge, it is unlikely that dementia will be reversed. Age is the most significant factor for developing dementia, which affects one in 20 people over the age of 65. In Germany, an estimated 900 000 persons suffer from dementia, 65-70% owing to Alzheimer's disease and 20% owing to vascular dementia. The remaining 10% is caused by schizophrenic psychoses and psychic disorders caused by drug and alcohol addiction (Korsakoff's encephalopathy).

Every year there are about 200 000 new cases in Germany. It is estimated that over the next four decades, the number of demented people will increase to at least 1.4 million if there is no breakthrough in the fields of prevention and treatment. It appears that in the major industrialised countries, between 6.5% and 8.7% of people over the age of 65 suffer from some kind of severe dementia. In Germany, the figure is about 7%. Annual costs are estimated at EUR 7.5 billion in institutional care and at EUR 2.5 billion in home care.

### *Shortcomings of the present LTCI programme*

One of the shortcomings of the new long-term care insurance scheme is said to be too narrow a definition of the range of people regarded as being dependent on care. First, LTCI seems to focus mainly on physical deficiencies affecting daily activities. Clearly, the picture is more complex. There are two main causes of dependency: illness and disability, both of which can be physical or psychological. As a result, a vast number of people (more than 50%) recognised by law as being in need of care suffer from some kind of dementia. There is nevertheless a growing public demand to broaden the legal definition of dependency so that more of those suffering from dementia can be beneficiaries of the Long-term Care Insurance Act. However, if the definition of eligibility is broadened, the costs would exceed the income obtained from the present 1.7% contribution. Increasing this contribution is generally regarded as impossible as it would further increase German labour costs and threaten the competitiveness of German industry in the European and global economy.

### *The proposals*

Within the existing financial limits, there is some scope for improving the situation for family and other informal caregivers who look after persons in need of long-term care and suffering from dementia. One proposal provides respite for caregivers by providing patients with a right to one day of care per week or four days per month in a day-care centre, without any deduction of the monthly care allowance. The three objectives of this approach would be: *i*) to reduce the burden of care for relatives, friends and other informal caregivers; *ii*) to improve or at least mitigate the condition of beneficiaries by offering professional level of care and rehabilitation in a suitable day-care centre; and *iii*) to foster the growth of day-care centres as a way to strengthen home care and avoid permanent institutional care and hospitalisation.

At present there are about 13 000 places in day-care facilities, and only 9 000 are occupied. However, most users are suffering from dementia and require long-term care. Notwithstanding the financial restraints mentioned above, the reserves and the annual revenue of the long-term care insurance funds would be sufficient to make an annual EUR 250 billion available for the project. That would be enough to benefit about 130 000 people.

The second proposal offers, as an alternative to formal care in a "full-fledged" day-care centre, an informal type of care in a "lower threshold" setting. A considerable number of voluntary groups

(initiated by the German Alzheimer Society and other voluntary organisations) offer care in a more informal family-oriented surrounding. Some of the *Länder* governments already foster these often quite imaginative initiatives by granting funds to supplement voluntary efforts. The ministry's proposal is to "co-finance" such projects, thus making more funds available. In addition, the ministry is considering introducing an "experimental clause" into the LTCI Act, which would allow the care insurance funds to finance (and thereby try out) innovative care projects. A third proposal would be to expand on the present home advisory services.

The proposals of the German Health Minister are based on an underlying philosophy of person-centred care. It cannot be denied that many of the ills experienced by people with dementia are not the result of their disability, but of negative attitudes and poor care practices. Where the quality of care is high, the experience of dementia need not be so negative; despite the loss of cognitive skills, people with dementia are still left with a capacity to enjoy life. This is the very same philosophy that led to the development of the Dementia Care Mapping scheme in Bradford (Yorkshire, England); the "Door Opening Approach" developed by the KDA – the *Kuratorium Deutsche Altershilfe* (the German Trust for Helping the Aged); and various initiatives launched by the German Alzheimer's Society, Alzheimer's Disease International and other national and international voluntary organisations. A person with dementia continues to be a person of worth and dignity, deserving the same respect as any other person.

There is currently no cure for dementia, but we can help people with dementia live as good a life as possible. Caregivers and health-care professionals have a crucial role to play in sustaining that quality of life. The German Health Minister firmly believes that the invaluable work of the many informal and professional caregivers and the numerous voluntary organisations should be backed up by progressive legislation, including financial assistance.

## Outlook

From its very beginning, the European Union has had a social dimension. In fact, caring for the poor, the destitute, the sick and the frail has been an important part of the common European heritage. It seems that in all European countries and beyond, the tradition of solidarity is still very much alive. The moral drive to look after the frailest members of our societies continues and is even experiencing a renaissance. The fact that the European Union, the Council of Europe and the OECD have placed care for the frail elderly among their priorities is gratifying proof of this.

There are, of course, different ways of providing assistance to people in need of long-term care. The social insurance approaches preferred in the Netherlands, Luxembourg, Japan and Germany are only one avenue. There is nothing wrong with tax-financed schemes. It will be a long time before the different systems in Europe are harmonised, if they ever are. From a German point of view, there is no need for harmonisation. In many fields, Europe is often strongest when it relies on the national and cultural variety of its member states.

There is however one point which, from a German perspective, is still important to remember: health and care benefits are not economically useless welfare handouts. They are, like education and training, indispensable social investments in people. Most of the countries in Europe have relatively few natural resources. The same holds true for Japan. What makes our economies work is people's skills encouraged by massive social investment. In other words, it is health care (including long-term care), education, human skills and mobility that are the most important factors for economic growth.



In examining present and future care provision schemes and their impact on the quality and equality of care, it is important to bear in mind the two principles of solidarity and human investment. For both social and economic reasons, the OECD should be encouraged to take on the rewarding task of enhancing international understanding and co-operation in the field of care for the frail elderly, particularly those suffering from dementia. To adapt a saying by the 20<sup>th</sup> century German philosopher Ernst Bloch, as (political) analysts we have to take things as they are, but as policy makers we do not.

## *Chapter 22*

### **DISABILITY AND ACCESS TO CARE OF THE ELDERLY IN ICELAND**

*by*

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Iceland, a typical Western society with a population of about 280 000, is looking at strategies to deal with disability and long-term care for the elderly. Life expectancy in Iceland is among the highest in the world and has increased by one year every five years for the last 30 years. As elsewhere, the oldest old are the fastest growing segment of the population. Furthermore, the Reykjavik Heart Study showed that the cohort of young olds are now healthier than 30 years ago. In many ways Iceland, even though it is small, can serve as a prototype for other Western countries.

The benefits of healthy ageing are manifold: a happier population with less disability, less long-term care and lower health-care costs. The last year of life tends to be the most costly in terms of health-care costs. But the older the person is at death, the less costly the last year of life, as palliation takes over from cure. Individuals and societies have to invest to "compress" the period of mortality, morbidity and disability. The prevalence of chronic disease doubles every five years after the age of 70. Thus, if at the age of 70 the presence of a disease could be delayed by five years, the number of people with that disease at the age of 85 would be reduced by 50%.

In these times of preventive medicine, it is important to recognise that one medication, such as the ACE inhibitors, estrogens and statins, can affect many organs. For example, the primary indication for statins is to lower blood lipid levels to prevent atherosclerosis. However, these drugs also increase bone mass and there is some evidence that they even protect the brain. This gives great hope for the future of preventive efforts. What is disheartening is that current knowledge is not optimally used. This is true for major treatable risk factors for strokes and heart disease, such as hypertension, hypercholesterolemia and anticoagulation for atrial fibrillation. This is also true for osteoporosis, which can now be prevented, at least in part, with vitamin D, bisphosphonates and estrogens, and SERM-type medications.

One year ago, in the author's clinical service, four patients were seen the same week: *i*) a 67-year-old woman with serious osteoporosis and a vertebral compression fracture that was both painful and disabling; *ii*) a 77-year-old man with high blood pressure and elevated cholesterol, who had received an artificial limb, and who was prescribed statins and ACE inhibitors in an attempt to preserve his other leg; *iii*) a 73-year-old man with high blood pressure admitted for intracerebral bleeding who had aphasia and was paralysed on his right side; and *iv*) an 85-year-old man with hypertension and dementia, whose CT scan showed white matter changes and lacunae that explained his cognitive decline. These four patients are mentioned because one factor links them: they all had potentially preventable conditions, if we had used our current knowledge about diseases of the elderly.

Prevention of conditions that plague the elderly requires adopting a triple strategy for the entire population from birth to death. Primary prevention focuses on total life span, including *life in utero*, but it becomes more relevant from about the age of 15. Primary prevention focuses on such things as improving nutrition, exercise, immunisation, prevention of accidents, and education about the risks of smoking. Secondary prevention treats known risk factors – for example, elevated blood pressure, high cholesterol and low bone mass – in order to prevent the progression of disease. These interventions are most relevant for persons from 40 to 50 years of age. Tertiary prevention is relevant when a disease is already present. Examples are rehabilitation and geriatrics. This type of intervention is most relevant after the age of 70. All three prevention strategies are needed to serve the total population.

Besides prevention, defining appropriate care for the elderly is also of great importance. There have been some important initiatives in Iceland in this area during the last decade. First, a nursing home pre-admission assessment system was put in place in the early 1990s for gatekeeping. Previously, people would enter a nursing home when they were healthy “to be on the safe side” in case they subsequently became sick. Those who then fell sick in the community could not get in because the healthy were already there. Second, Iceland has also adopted the resident assessment instrument (RAI) for nursing home care to improve and pay for the care. A report has been written on prioritisation in health care, and work is under way on a policy for health care for Iceland to the year 2010. Development of clinical guidelines has begun, and an information and quality of care policy has been issued. Finally, a health-care intranet for all of Iceland is being developed to improve communication among all stakeholders in the health-care system.

The focus in clinical guidelines is on diseases which are common, high-risk and expensive; in addition, if they are brought under control, the well-being of patients will improve. For clinical guidelines to be cost-effective, practices that are cost-effective need to be accepted and seen as an investment in improved health. Thus far, the development of clinical guidelines has not delivered on all its promises. To improve their impact, it is necessary to study how best to motivate physicians to follow them. The psychology of professionals as well as of patients needs to be carefully studied as it relates to compliance with guidelines for diagnosis and treatment.

In addition to implementing these clinical guidelines, equal effort has to be given to monitoring and modification over time. A report on prioritisation published in 1998 has several components. It discusses ethics and emphasises equality of all people regardless of age. It also underlines the importance of health-care needs for determining national health insurance coverage. The prioritisation process dictates that all new medical equipment and methods of treatment shall meet standards of effectiveness and safety. To this end, an interdisciplinary committee has been established to deliberate on the adoption of new services. Further, it was decided that, on average, the health services should spend 3-5% of its yearly budget on new technological development. The report also places great importance on developing health information systems for the future and strengthening quality assessment and standards. Finally, it supports a strong initiative in preventive medicine.

Icelandic health policy to the year 2010 was debated in Parliament, including a discussion on defining objective measurable goals. There was a conscious effort to set realistic health goals that can be achieved by applying existing know-how. Examples of the goals include: reduction of smoking among those 18-69 from 27% in 1998 to 15% by 2010; reduction of cardiovascular deaths among those 25-74 by 20% for men and by 10% for women; reduction of strokes by 25%; reduction of the number of hip and vertebral fractures by 25%; and a goal that more than half of those 65 and older should have at least 20 healthy teeth. Most of these measurable goals will have spillover effects and improve the healthy ageing of the population. If these goals are attained, an estimated 75% of people aged 80 and older should be able to live in their own homes.

The nursing home pre-admission assessment is an evaluation performed by a multidisciplinary geriatric team with a view towards rehabilitation and support to enable the elderly to live at home. Only those who cannot stay at home are given a certificate of need for placement in a nursing home. The evaluation is standardised and includes assessment of social, medical, cognitive and affective factors in addition to an evaluation of the ability of the individual to perform the primary activities of daily living unassisted. From this assessment exercise, the Icelandic government reached a clear understanding of its long-term care needs. There is now a national waiting list for placement in nursing homes based on the needs of the individual. In 1994, for example, we knew that 15 out of 1 000 elderly people were truly eligible for nursing home care. Adjusted for sex and age, women were more likely than men to need nursing homes. Not surprisingly, although it was startling at the time, 78.5% of those waiting for a nursing home have dementia. Imagine the social impact of conquering dementia.

The resident assessment instrument (RAI) for nursing home care was mandated in Iceland in 1996 and was pilot-tested in 1997. A mental-health instrument is also being tested and Iceland will participate in a ten-nation European study, and the acute-care instrument will be studied in all the Nordic countries. In addition, there are interesting instruments for dealing with post-acute care, and one on palliative care is being planned. These various RAI instruments are also called minimum data sets (MDS) as they utilise micro-level assessment data of individual persons. Care plans are developed on the basis of the assessments, as are case-mix algorithms, quality indicators and outcome measures. The RAI or MDS tools are valuable and multifunctional. The RAI system is being evaluated in many countries around the world. It originated in the United States, has been adopted widely in Canada, and many European countries and Japan are actively studying this approach.

Those who work with the RAI system visualise an integrated, seamless, health information system, where RAI data could flow from one setting to the next. This is made possible by a common core of assessment items and specific site-linked items or variable parts specific to each setting. The common core of information thus travels with the patient through the system as he or she moves from one stage to the next. The RAI system is integrated by its common language and consistent technology across the instruments. There is a common theoretical conceptual basis, the "triggers for care" plans which are based on assessment of the individual. The emphasis is on clinical and functional assessment rather than diagnosis. All the instruments have common core elements which allow patient groups to be split according to activity of daily living and cognitive function, as well as allowing comparisons across systems and nations.

Some interesting questions can be raised when the RAI system is used internationally. How does one country compare to another in its care of the elderly? How close are we to achieving optimal performance in our respective health-care systems? A pilot study carried out between 1992 and 1994 used nursing home RAI data to compare population data from Copenhagen, Reykjavik and four cities in the United States. It found that 32% of elderly people in nursing homes in Iceland were disabled compared to 53% in the United States and 36% in Denmark. These data were collected from the nursing home population before the effects of the nursing home pre-admission assessment system were apparent. Thus the elderly in Iceland functioned better in terms of daily living than their contemporaries in the United States and Denmark. Iceland should thus consider the possibility of improving home care rather than adding nursing home beds. Further international studies may enable one country to learn from another about how to improve its system.

The RAI system will help to develop quality indicators of care. For example, depression is prevalent, under-diagnosed and under-treated in the nursing home setting, leading to a poor quality of life. The share of people with untreated depression was 23% in Iceland compared to 43% in the United States and 45% in Denmark. In this sense Iceland fared better than the other nations. However, Iceland

makes excessive use of psychotropic drugs in the nursing home population: 74% compared with 44% in Denmark and 29.5% in the United States. Iceland also uses a greater amount of hypnotic medications at night.

There are roadblocks to improving healthy ageing in Iceland. To begin with, individuals are insufficiently educated about measures that can prevent disease or improve the likelihood of good health. There is also a residual, albeit dwindling, ageism by society and even among health-care professionals. Another difficulty is that physicians are not optimally motivated to follow guidelines and patients do not comply with advice. This is a universal problem and ways must be found to improve health habits. Politicians and physicians tend to take the short-term view and prioritise financing and delivering acute health care over the long-term view of prevention. There is a tendency not to see the forest for the trees.

Nations and individuals need to invest in good health and use the triple strategy of prevention mentioned above. Investment in healthy ageing as part of current health-care costs will have pay-offs in the long run. To improve the implementation of guidelines, the development of clinical guidelines needs to include psychological factors. Iceland benefits from an integrated information system with standardised data collection, such as the nursing home pre-admission assessment system and the multifunctional RAI system; these systems help to assess the quality of care in nursing homes and the necessary funding. The cross-national comparability of the data is a bonus.

Finally, more research is needed, both in Iceland and elsewhere. The basic factors of disease or the key points and common pathways for many conditions need to be identified. This would open up the possibility of developing treatment for multiple conditions simultaneously and reducing the tendency towards polypharmacy. In future, preventive efforts will perhaps be better targeted, based on genotyping of individuals. Apart from basic scientific development, optimised collection and management of data are needed to make informed decisions about the care of the elderly. In our search for technological improvements, however, we must not overlook the human factors, be they the patients or professionals.

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## **V. HEALTHY AGEING AND BIOTECHNOLOGY – BEYOND THE TOKYO WORKSHOP**

This section looks beyond the economic and scientific contributions in this volume and turns to the ethical and social trends that will make the task of addressing the needs of the elderly ever more challenging. Social ambivalence towards supporting an older society, the gap between the rich who can afford elective treatment and the poor who may be forced to accept more limited treatment of their ills later in life, the increasing political power of those over 65 are only slowly being acknowledged and debated in OECD countries. Nevertheless, some groups have been quicker to recognise the importance of elderly health, with academic researchers and the pharmaceutical industry at the forefront. Governments need to study these trends and develop future scenarios for spending on their ageing populations if they want to shape the terms of debate on what constitutes healthy ageing.

## *Chapter 23*

### **BEYOND THE TOKYO WORKSHOP**

*by*

**Salomon Wald**

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#### **The Tokyo Workshop**

The OECD Workshop 2000 on Healthy Ageing and Biotechnology covered an unusually large and diverse range of subjects. The scientific and medical opportunities presented ranged widely and included many fields of medical and biological research. Participants pointed out that the health conditions and mortality of the elderly result from both their genetic inheritance and environmental exposure and are profoundly affected by diseases they have suffered during their entire lifetime, even before birth.

The workshop reviewed genetics and genomics, molecular and cellular biology, and gave great attention to progressive cognitive impairment (Alzheimer's disease, Parkinson's disease), problems of mobility and frailty, vascular diseases and cancer and the potential contributions of biotechnology in alleviating these diseases. Participants emphasised the importance of prevention, early diagnosis and early intervention and presented a vision of a not too distant future when undesirable aspects of ageing could be prevented, arrested or even reversed.

Economic, social, and ethical questions and considerations were given as much time as biomedical ones. The discussion of economic problems raised by ageing and its interaction with biotechnology was extensive and more narrowly focused than the science sessions. The economic burden of ageing and age-related diseases on governments and the public sector was the single most frequent theme. This is natural as health expenditures of the elderly absorb 40-50% of national health budgets. The workshop aimed at providing useful data for OECD governments struggling with rising public health costs. As organisers and participants wanted to get the attention of governments, they addressed cost and budget issues. Inevitably, concerns about the increasing and the less and less affordable costs of health care for the elderly tended to focus many of the discussions on short-term aspects.

Ethical and social aspects were also much discussed, ranging from consumer information and social consensus on ageing, to equitable access to care, to exclusion and rationing. The discussions on policy conclusions and recommendations to governments included science and technology policy goals: how to target R&D to the needs of the elderly? how to reduce roadblocks to the development and diffusion of new technologies?



However, the main emphasis of the recommendations was on economic, social and ethical issues:

- ♦ The increasing burden of health care for the elderly will make it necessary to reassess how health-care costs are financed and distributed.
- ♦ Regulations, which too often lag behind science, must be better adapted to new technologies and the needs of the elderly.
- ♦ The treatment of the elderly should be fair and ethical and must include an effort towards greater equity of access to health care.

Contrary to what one might have expected, the question of ageing, a problem as old as life on Earth, turned out to be as controversial and divisive as the most “avant-garde” health issues raised by biotechnology, such as genetic testing, gene therapy or stem-cell research. More than once discussions became tense and strong political sensitivities emerged; a middle ground was difficult to find. Ideological and ethical commitments, the politicisation of public health-care systems, and the need for policy makers and regulators to watch carefully what is politically acceptable and what not, explain some of these sensitivities. Hence, some underlying themes were not touched upon, some questions were not openly discussed, some opinions were not heard, and some contradictions were not raised.

The following reflections are a personal view and not an exhaustive summary of the workshop. They indicate some of the underlying problems which have not been discussed, or not extensively, but deserve to be raised.

## **Unresolved questions**

### ***What is the link between biotechnology and healthy ageing?***

Biotechnology is increasingly being recognised as a pervasive technology that is penetrating all sectors of the economy and society. Many see this pervasiveness as comparable to that of information technologies. The first predictions of the coming developments date back to the late 1970s and early 1980s. However, there was then a long period where doubts about the technology’s apparently unfulfilled promises prevailed.

Since the start of the new century, controversies over genetically modified foods in many countries coincided with the highly publicised sequencing of the human genome. These and related events brought biotechnology to the attention of a much wider public. The linking of biotechnology to core issues such as ageing that will preoccupy humankind in the 21<sup>st</sup> century is a result of this new awareness. Also, as biotechnology and genetics are transforming virtually every field of medicine, it should not appear far-fetched to study the impacts of the new technologies on specific health issues.

Still, some resistance was felt to the workshop proposal during its preparation. Was it really necessary to link everything under the sun to biotechnology? Was the link to ageing genuine and convincing or somewhat contrived? The link seemed fuzzier than the link to the agro-food sector or to human health in general, or to more specific health problems such as infectious diseases or genetic disabilities.

In the latter cases, the importance of the new technology is obvious. However, in the case of ageing, the relationship has many different components, some of which provide an indirect link at best. For example, presentations were given on improving the mobility of the elderly by artificial joints such as knees – here, the link to biotechnology is that knees are constructed from new materials

based on biotechnological processes. This link is much more indirect than for example, the important and obvious contributions of biotechnology, particularly genomics, to the fight against infectious diseases.

Thus, the broad and sometimes indirect nature of the relationship explains some of the difficulties involved, including those of formulating a unified set of simple and compelling policy conclusions.

### *Is ageing good?*

From time immemorial, humans have been ambivalent, to say the least, towards old age and ageing and have dreamt of immortality. Not all civilisations and philosophies have seen ageing, even healthy ageing, as a good in itself. This ambivalence continues perhaps to influence the debate. When workshop participants discussed whether recent genetic discoveries might open up the theoretical possibility of immortality or of extending the human life span to say, 200 years, did they discuss ageing – or how not to age?

In Greek mythology, a grateful mother prayed to the goddess Hera to reward her two sons for their good deeds with the most beautiful gift that the divinity could confer on mortal humans. Her sons collapsed and died on the spot – for dying suddenly, young and vigorous, was a more desirable fate than lingering on until old age. When young prince Siddharta Gautama, before he became Buddha, left his father's palace to explore the world outside, he saw for the first time an old, a sick and a dead person as well as a holy man and thus discovered that life was mere suffering. Note that the old and the sick were not the same person: the old man was a "healthy elderly", but the mere view of old age came as a shock. And Hungary's great national poet, Sándor Petőfi, asked God in his most famous poem of 1847, two years before he was killed by enemy hands at the age of 29, not to let him waste away in bed to die old and sickly but to let him leave this world, like "a tree split by a thunderbolt", or felled in battle for freedom. There are many other examples.

Of course, the main tradition that is diametrically opposed to such views is the biblical one, where life is precious and living to a ripe old age a great and most desirable gift. This tradition, linked to respect for old age, prevails elsewhere as well, such as Confucian China and Japan.

Past or current ambivalence about ageing may affect general attitudes and even policy discussion of possible contributions by biotechnology. The workshop noted that Alzheimer's disease, which afflicts large numbers of the elderly, has so far attracted much less public interest and R&D support than AIDS, which largely afflicts the young, although many more people are suffering from Alzheimer's disease than from AIDS. France, for example, expects for the year 2002 fewer than 2 000 new cases of AIDS but more than 75 000 new cases of Alzheimer's disease. It is universally agreed that better health in general, a cleaner environment, better crime detection and the possible contributions of biotechnology to all these, are good. Is ageing different? Is it possible that the lesser attention paid to the diseases of ageing reflects a hidden prejudice?

### *Is biotechnology for healthy ageing "politically correct"?*

Policies in every field, in the OECD area and beyond, are most easy to justify when they conform to written and unwritten postulates of "political correctness". Politicians forget this at their peril. Now, how would biotechnology for healthy ageing enhance the main political agendas?

### *Closing the gap between rich and poor*

It is not evident that biotechnology for healthy ageing will help to close gaps between the rich and the poor. This may be politically unappealing, but in the short and maybe even in the medium term, healthy ageing appears the rich world's concern and privilege. Currently, those who enjoy generally better access to health information and care have a greater chance to reach old age. When old, they will be in a better position to afford more expensive health technologies and care. In other words, to be well to do, to grow old and remain healthy, are to some extent correlated in a kind of "virtuous circle".

Will this remain so in the long term? If treatment and drug costs come down considerably, and if health information is more widely disseminated, the poor may benefit from biotechnology no less or not much less than the rich. While this will prolong the life of many millions compared to their present conditions, it does not mean that the health or mortality gap between rich and poor will close substantially. There is no foreseeable limit to technological and medical progress, and the biologically possible lifespan for humans is now said to be much longer than once anticipated. Therefore, there will always be newer and more expensive treatments and technologies from which the rich will be able to benefit first.

### *Do these arguments apply also to the gap between the rich and poor countries?*

Participants at the workshop were very sensitive to this question. It was emphasised that in little more than 20 years, 60% of the world's elderly will live in Asia. Can it be inferred that biotechnology for healthy ageing will be good for the poor and developing countries as well? Developing countries differ considerably. Ageing will become a major issue for some within a generation (China is most often mentioned in this respect). There is a fundamental historical difference between ageing trends in Western countries and those in today's developing countries. In the West, trends began to rise slowly and incrementally more than 100 years ago. Society and governments had time to adapt. In third world countries, trends accelerated only after World War II and are now rising much faster than in the West. These countries have much less time to prepare themselves for an ageing society. It must be hoped that biotechnology will be able to make a substantial difference to the health situation of the elderly in these countries.

However, statistics cannot obscure the fact that while biotechnology innovations may help many elderly citizens of poorer countries – at least those who can pay for them – it will not address the more pressing health concerns of many others: infectious diseases (water-borne infections, malaria, tuberculosis, AIDS, etc.) are among the most urgent. Many poor countries have to deal with health priorities that are not directly related to ageing and the diseases of the elderly. Another urgent health issue is malnutrition among children, which is widespread even in some of the least deprived third world countries. The prognosis for malnourished children to remain healthy as they grow older is not good, to say the least. Paradoxically, it could be said that in some countries one of the most effective long-term contributions of biotechnology to healthy ageing would be to provide more and better food and health care to malnourished children.

### *Democratisation and greater equity*

It follows partly from the above that it will not be easy to bring the postulate of fair and equal access to technologies for healthy ageing in line with competing demands for limited health budgets. It was agreed at the workshop that fair and ethical treatment of the elderly would call for greater equity of access to health care. This will be difficult but not impossible to achieve in the long run if it is

limited to the elderly, rich or poor, in the OECD area. But how to reconcile the health needs of the elderly in poorer countries with those of the young, millions of whom die of preventable or curable diseases every year? When resources are limited and biotechnology for healthy ageing has to compete with biotechnology for sick children? If dramatic choices have to be made, they will not often be in favour of the elderly.

### *Human rights*

Here the link is much more positive. Biotechnology for healthy ageing can easily be defined as enhancing “human rights”. The general human rights concept has diversified into rights for a growing number of groups: workers’ rights, women’s rights, children’s rights. There is probably no agreed list yet of “human rights of the elderly” as there is of “children’s rights”, but the formulation of such a catalogue would be justified and is perhaps only a question of time.

## **The main forces driving biotechnology for healthy ageing**

### *The first force: academia*

Three forces or actors can drive and fund biotechnology for healthy ageing: academia, government and industry. Biotechnology was born in the university, and many of the crucial advances and breakthroughs still come out of universities. It is therefore logical to start here. The “science push” of the last few years has dramatically improved our understanding of the fundamental mechanisms of human ageing and has given new instruments for the early diagnosis, prevention and, in some cases, cure of age-related disabilities. The number and power of these instruments keeps growing. Advances in genetics and genomics, in molecular and cellular biology (such as stem-cell research) will probably in less than 20 years lead to a revolution in medical prevention and treatment, with enormous positive consequences for the elderly.

“Biotechnology for healthy ageing” benefits from these advances in many ways, direct and indirect, but as such, is rarely a priority target for academic research. Biological and biotechnological disciplines are targets and so are many specific age-related diseases. Academia alone is not likely to drive this field forward; the intervention of the two other actors, government and industry, is essential.

### *The second force: government*

Government has many instruments, direct and indirect, with which to affect the progress and direction of biotechnology for healthy ageing. R&D funding is the main direct instrument, regulatory and taxation policies the main indirect ones. Like academia, government will fund biotechnology R&D and develop policies with regard to the elderly, including technology policies, but they will rarely choose “biotechnology for healthy ageing” as a specific goal for public policy.

Prof. Robert Fogel of the University of Chicago suggested at the workshop that health care, particularly for the elderly, should not only be seen as an expenditure or as “consumption”, but rather as a long-term “investment” from which countries will reap considerable benefits in terms of economic growth. During the last 100 years, better health has been a major factor in economic growth. Such a major change in perception could bring about a radical reassessment of public health expenditures: rather than dreading the predicted rise in national health expenditures in the United States, for example, from the current level of 14% of GDP to 21% in 2040 and viewing this only as a

source of growing fiscal pressures, governments and the public should welcome this rise because it is a precondition of continuous long-term economic growth and prosperity. The financial planning and vision of governments, however, look at the short term, not the long term. The muted, if not anxious reaction of some health-care officials to Prof. Fogel's suggestion made it clear that in the foreseeable future, governments are not very likely to adopt his long-term vision. This means that the main initiative to support biotechnology for healthy ageing in the long term may have to come from the third actor, industry.

### ***The third force: industry***

It was revealing to observe the keen interest of large pharmaceutical companies in the workshop, something that could not be said of all OECD governments. In fact, this industry has more incentives and freedom than academia or governments to choose biotechnology for healthy ageing as a priority area. Such a choice requires a long-term commitment to fund R&D. Big industry can usually afford commitments which last ten years or longer with greater ease than the other two actors, as long as market signals are encouraging. In this case, market incentives may be large. The market for diagnostic, preventive and therapeutic products to deal with age-related health conditions is already large and will grow steadily as populations continue to age.

More importantly, the elderly represent a comparatively "docile" market. Many currently live in the richer countries, and so does the overwhelming majority of the elderly who can afford expensive products. This is an attractive prospect for the pharmaceutical industry, which has come under increasing pressure from third world countries and militant groups in the West. The industry is being asked to lower the prices of drugs of particular importance for poorer countries and patients (such as AIDS or malaria drugs) and/or to reduce or abandon the intellectual property rights which it has considered indispensable for long-term investment. Important companies have been forced to compromise on these issues. In contrast, it is most unlikely that any Western capital will soon see vocal street demonstrations of the elderly, protesting against globalisation or the patent rights of the pharmaceutical companies.

Governments are not unaware of the drug industry's potentially great interest in this area and can exploit it. For example, in 2000, the Japanese government created a new long-term care insurance system to turn the private sector into a more important supplier of care for the elderly. Also, industrial support for academic research in the biological, chemical and medical fields might be induced to give particular attention to diseases of the elderly.

This means that the private sector will probably have a great and increasing influence on the rate and direction of technological and perhaps also scientific progress related to healthy ageing. To some extent, private industry, through its R&D decisions and investment, will become a major arbiter of who will live to old age and who will not. Industry will make many of the critical choices between diseases that might become preventable or treatable in a foreseeable future and others that will not.

Is this a worse outcome for the interests of the elderly in affluent countries than greater government control over technological innovation? Not necessarily. The history of pharmaceutical innovation during the last 100 years does not indicate that the interest of the public in better health treatment was less well served by private industry than by government, and it is not difficult to argue that sometimes the opposite has been true.

If the trend predicted here materialises, the multinational pharmaceutical industry may once again be criticised for helping to increase the gap between rich and poor. However, it will be important for

governments and the public to understand that this is probably inevitable, as it reflects the current interplay between strong market forces and weaker or less targeted government policies.

### Developing future scenarios

Governments have been much worried about the financial burdens of ageing. There has been less effort to look for possible benefits as well as costs. Professor Fogel does not share the lugubrious economic view of ageing, but he is still an exception rather than the rule. Some sociological research on the possible future shape of "greying societies" has been carried out, but the broader, long-term implications of present scientific and technological progress pertinent to healthy ageing were not mentioned at the workshop.

In fact, it would be useful to develop future scenarios for the evolution of societies increasingly dominated by a large number, if not a majority, of the "elderly" as they are currently defined. Such scenarios must remain tentative and open-ended because the number of variables to be considered is very large, and so are the possible interactions among them. Scenarios would probably indicate that some current concerns are exaggerated, such as the fear that the working population might not be able to continue financing the retirement pensions when the number of pensioners is larger than that of wage earners. Scenarios could also point to possible major crises, ruptures or backlashes not imagined today.

A few trends seem obvious. The political power of the elderly will increase considerably. How will they use this power, if at all? In the past, voting patterns of the elderly have apparently often been conservative, supporting more "traditional" values, rejecting innovation and experiment. Will this be true in the future? With the promised radical improvements in health conditions, including mental health, the "elderly" of the future may have little in common with the "elderly" of the past.

Another likely trend relates to the job market. If traditional age-related health burdens, particularly cognitive impairment, can be delayed, prevented or even reversed, there will be no health- or age-related justification for legally imposed retirement. It is possible that more and more countries will abandon compulsory retirement, yielding to the new political power of the elderly. What will be the consequences for work, education and leisure? Will a growing number of dynamic, healthy, mentally fit and professionally very experienced elderly block the lives and stymie the careers of the young, who will be equally dynamic and fit, but certainly less experienced? What lies in the future? A severe generational conflict, a revolt of the young, or new and more flexible ways of organising and sharing work, education, retirement and leisure?

Other changes may be more far-reaching. One question raised by the delay of old age and more healthy ageing relates to the reproductive abilities and desires of both men and women. The workshop could have discussed the changing medical and biological conditions of human fertility but did not. Anecdotes of famous or rich men who father children at the age of 80 or more or of women who give birth at the age of 50 or 60 appear with some regularity in the media, but are treated as eccentricities and are usually frowned upon.

What does the long-term future hold? Will the health and reproductive ability of the future elderly of 70, 80 or 90 years resemble those who are 30 or 40 year old today? Will they claim the right to have children? What will be the legal, social, ethical implications of the reported longevity of the legendary early patriarchs of the Bible who had children at a very advanced age? There are other religious myths, but no human memory of such conditions. With so much to imagine and prepare for, the Tokyo Workshop will certainly not be the last of its kind.

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